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ARACHNODACTYLY AND ITS MEDICAL COMPLICATIONS

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Although there are at present in the neighborhood of two hundred reported cases of arachnodactyly, the syndrome is little known to the members of the American medical profession. Most of the literature is in French or German, and in this country few but ophthalmologists are familiar with the condition. Since arachnodactyly should interest orthopedists, pediatricians and physicians in general, as well as ophthalmologists, we wish to summarize its characteristics and report two cases with particular reference to the medical complications.

Described first, in 1896, by Marfan [1] as "pattes d'araignée" or "dolichosténomélie," the condition acquired the more familiar name arachnodactyly (spider fingers) from Achard [2] in 1902. The first case recognized in America was described by Piper and Irvine-Jones,[3] in 1926. Comprehensive articles on arachnodactyly have been published by Young,[4] Ormond,[5] Weve,[6] and Burch.[7] The syndrome is familial and congenital, with the following major characteristics:

1. Abnormally long gracile fingers and toes
2. A decrease in the usual amount of subcutaneous fat
3. Generalized underdevelopment of the musculature
4. Relaxation of the ligaments

From the Department of Medicine, Johns Hopkins Hospital.

1. Marfan, A. B.: Un cas de déformation congénitale des quatre membres, plus prononcée aux extrémités, caractérisée par l'allongement des os avec un certain degré d'amincissement, Bull. et mém. Soc. méd. d. hôp. de Paris **13**:220-226 (Feb. 28) 1896.

2. Achard, C.: Arachnodactylie, Bull. et mém. Soc. méd. d. hôp. de Paris **19**:834-840 (Oct. 10) 1902.

3. Piper, R. K., and Irvine-Jones, E.: Arachnodactylia and Its Association with Congenital Heart Disease, Am. J. Dis. Child. **31**:832-839 (June) 1926.

4. Young, M. L.: Arachnodactyly, Arch. Dis. Childhood **4**:190-214 (Aug.) 1929.

(Footnotes continued on next page)

In addition each of the following characteristics is found in 50 per cent or more of the cases:

5. Bilateral dislocation of the lens, with a tremulous condition of the iris (iridodonesis) and contracture of the pupil (not dilating normally under the influence of atropine sulfate)

6. Congenital abnormalities of the structure of the heart

7. Prominent ears

8. A highly arched palate

9. A tendency to infantilism

10. Kyphosis, scoliosis, deformities of the sternum and asymmetry of the thorax

11. Deformities of the joints, especially of the feet, with associated contractures

Marfan's syndrome is commonly noted in children. The diagnosis is made almost at a glance. The patient is usually tall and at the same time underweight for his age. The extremities are increased in length disproportionately to the stature. As Young [4] has demonstrated, this is due to a marked increase in length of the metacarpals, metatarsals and phalanges, without a proportional increase in the diameter of these bones. Thus the hands and feet are abnormally long and narrow. Often the fingers are slightly webbed. At the same time the musculature of the arms and legs is markedly underdeveloped, and there is practically no subcutaneous fatty tissue. As a result, all bony prominences are marked, and emaciation accentuates the length of the extremities and enhances the slender spidery appearance of the arms and legs. To complete the picture, there is marked hypermotility of the joints of the extremities, owing to the relaxation of the ligaments; the patella can be partially dislocated at will, and often the fingers can be contorted into grotesque positions. There is no evidence of amyotonia, and the efficiency of the muscles is normal. Frequently there are secondary contractures. Full extension of the fingers is sometimes impossible. Flat foot, hammer toe and clubbing of the foot, similar to that seen in Friedreich's ataxia, are all common. Roentgenograms of the skeletal system reveal long, narrow bones, with no evidence of periosteal bone formation commensurate with the increased epiphysial activity, a finding contrary to that in acromegaly. Some authors describe evidence of actual decalcification, but the few studies in which the calcium and phosphorus metabolism has been reported have

5. Ormond, A. W.: The Etiology of Arachnodactyly, with Special Reference to Ocular Symptoms, Guy's Hosp. Rep. **80**:68-81 (Jan.) 1930.

6. Weve, H.: Ueber Arachnodaktylie, Arch. f. Augenh. **104**:1-46 (May) 1931.

7. Burch, F. E.: Association of Ectopia Lentis with Arachnodactyly, Arch. Ophth. **15**:645-679 (April) 1936.

revealed no abnormalities. In a few cases spina bifida occulta has been revealed roentgenographically.

The patient, as a rule, is moderately dolichocephalic. The large ears stand out prominently; the auricular cartilage is often imperfectly developed and gives poor support to the soft tissue. The face is long and thin, with a tendency to frontal bossing and prominence of the supraorbital ridges. The palate is high, and the teeth are sometimes irregularly placed. The jaw is long and often prominent and tends to droop, giving the subject a somewhat adenoid facies. The long face and glasses, which many of these children must of necessity wear, lend an air of premature senescence.

The eyes are deep set. The ocular defect when present is characteristic and a great diagnostic aid, but it should be emphasized that it is not necessary for the diagnosis. It consists of congenital bilateral dislocation of the lens, complete or incomplete and generally upward. When the lens is in the anterior chamber, glaucomatous phenomena are usually encountered. The lens itself shows a diameter that is less than normal, and it tends to be spherical, perhaps because the defective suspensory ligament no longer exerts its usual centrifugal force. Myopia is common, and vision is considerably impaired. The iris is left unsupported by the lens; consequently, tremulous wavy motions of the iris are noted when the patient turns his eyes rapidly from side to side. Unless obstructed by the displaced lens, the pupil is small and the reactions are limited, ostensibly owing to fibrosis of the iris rather than to a fault in the dilator muscle.

Probably as a result of the inadequate musculature and the ligamentous relaxation, spinal kyphosis and scoliosis of a marked degree of severity are common. Similarly, the anterior portion of the chest is misshapen, with pigeon breast or funnel chest and asymmetry of the two halves of the thorax.

Infrequently, the patient becomes cyanotic or dyspneic on exertion and is limited in his activities on that account. A history of cardiac symptoms is not the rule, however. On examination the cardiac dulness may or may not be increased. In some cases there has been noted increased dulness to the left of the sternum in the second and third interspaces, and this increase in cardiac dimensions has been corroborated teleroentgenographically. Interpretation of the cardiac shadow on the roentgenogram is usually difficult, however, owing to the presence of scoliosis and consequent asymmetry of the chest, with displacement of the heart. On auscultation, loud precordial systolic murmurs are common, in some cases loudest at the apex and in others at the base of the heart to the left of the sternum. More rarely, presystolic apical murmurs or diastolic murmurs heard along the left border of the sternum

have been described. These findings may suggest rheumatic heart disease, but three of the four patients who have come to autopsy have shown interauricular septal defects.

Finally, there is ordinarily a tendency to infantilism, with delayed development of secondary sexual characteristics, and often the basal metabolic rate is decreased. Values as low as —25 and —30 per cent have been recorded, but in view of the striking abnormalities of bodily configuration found in arachnodactyly, it seems likely that an element of error may enter the calculation of the metabolic rate when the findings are referred to the usual caloric tables based on height, weight and surface area.

The disease is hereditary and has been thought to be transmitted as a dominant mendelian characteristic. No definite racial proclivities have been described. The disease has, until lately, been known more generally to French and German physicians than to those of other countries, and therefore the majority of cases have been reported in families of European stock. Arachnodactyly occurs in the Negro; we have recently seen a Negro and three of his children, all with dislocation of the lens and other stigmas. The trait may be transmitted through either the mother or the father; consanguineous marriage was reported in few of the families. In the majority of instances stigmas of the syndrome have been noted in a parent or in brothers and sisters of the patient when the family was large; only a few cases have been reported as isolated instances in a family. The hereditary element becomes more apparent when it is realized that in large families formes frustes are the rule.

While it is not uncommon for all the major characteristics of the disease to be found in a single case, more often one or more of them are missing. Probably the most common abnormalities are the tall emaciated figure, the long slender fingers and the deformities of the spine and chest, these changes being noted in almost all cases. From combined statistics, the incidence of the other stigmas in patients with arachnodactyly is found to be somewhat as follows: ectopia lentis in 40 to 50 per cent, abnormalities of the external ear in 25 to 70 per cent and cardiac murmurs in 30 to 60 per cent. Thus, although such striking abnormalities as bilateral displacement of the lens or a loud precordial systolic murmur often are absent, the finding of long gracile extremities and other pronounced stigmas is considered sufficient for a diagnosis of arachnodactyly, particularly if the missing traits are present in other members of the family. The second of our two patients showed only the typical extremities and scoliosis; there was no familial history of symptoms of arachnodactyly other than that a first cousin had arachnodactylic fingers.

The fingers and toes are long at birth, and this feature is usually observed by the parents. The infant mortality for these patients is reputedly higher than it is for normal infants. Throughout childhood and adult life the arachnodactylic person has an inferior gross physical strength and is more often subject to infection of the upper respiratory tract and to other minor ailments. The intellectual faculties are normal. As the growing child begins to walk and become more active, the deformities of the spine and chest develop. When these are well established, they render intrathoracic disease additionally dangerous. Pneumonia in particular is a scourge and is the commonest cause of death among these patients.

The etiology of arachnodactyly is unknown and is vigorously debated. To early writers, before the hereditary nature of the disease was established, the characteristic findings of ligamentous relaxation and congenital heart disease suggested a similarity to mongolism. However, the theory of faulty gestation after maternal reproductory fatigue has been discredited. The arachnodactylic person is now generally recognized as a genetic sport, various mesodermal elements of the body structure having been affected in the early weeks of fetal life. Thus Weve [6] would substitute the name congenital mesodermal dystrophy for the less comprehensive term arachnodactyly. There is discussion, however, as to whether a purely mesodermal fault could cause the defects often observed in the suspensory ligament of the optic lens. François,[8] while considering the dystrophy mesodermal, regarded the hypophysis as its specific cause and suggested that it may be a form of fetal gigantism. Passow [9] expressed the belief that the condition has a neurologic basis allied to that of syringomyelia, calling attention to the somewhat similar skeletal deformities noted in the so-called status dysraphicus sometimes associated with syringomyelia. Young [4] observed that the symptoms of amyotonia congenita are occasionally associated with those of Marfan's syndrome, and he postulated a common origin for the two diseases.

The four patients that have come to autopsy offer no solution to the etiologic problem but corroborate the presence of cardiac and pulmonary abnormalities. Salle's [10] patient, a 6 week old boy, had an enlarged heart with a hypertrophied right ventricle and a patent foramen ovale;

8. François, cited by Delord, E., and Viallefont, H.: Luxation héréditaire du cristallin et syndrome de Marfan, Bull. Soc. d'opht. de Paris, January 1936, pp. 44-55.

9. Passow, A.: Analogie und Koordination von Symptomen der Arachnodaktylie und des Status dysraphicus, Klin. Monatsbl. f. Augenh. **94**:102-103 (Jan.) 1935.

10. Salle, V.: Ueber einem Fall von angeborener abnormer Grösse der Extremitäten, Jahrb. f. Kinderh. **75**:540-550, 1912.

before death a loud systolic murmur was heard at the apex and in the pulmonic area. There was a bony exostosis on the floor of the sella turcica, but the hypophysis was normal save for a diffuse increase in the number of eosinophilic cells. Börger [11] reported an autopsy on a girl aged 1 year with physical findings typical of arachnodactyly, including a loud systolic murmur audible at the apex and at the base and transmitted all over the chest. Necropsy revealed that the heart was of normal size, with a patent foramen ovale. The middle lobe of the right lung was vestigial. In the anterior lobe of the hypophysis were several small cysts, and again the number of eosinophils seemed increased. The third patient, reported on by Piper and Irvine-Jones,[3] was a girl of 21 months who had a systolic thrill and presystolic and systolic murmurs at the base of the heart. Autopsy revealed a deficiency in the interauricular septum. The middle lobe of the right lung was extremely small; the left lung consisted of a single lobe. The hypophysis was normal. A fourth patient, soon to be reported on by Rambar and Denenholz, had no congenital cardiac or pulmonary anomalies, and the hypophysis was considered normal.[12] The first three patients died of pneumonia; none showed a congenital abnormality of the cardiac valves.

In the absence of a satisfactory explanation as to the cause of the disease, treatment must be purely symptomatic. Orthopedic exercises and braces may ameliorate the various skeletal deformities, and successful removal of the dislocated lenses will, with proper correction, restore a fair degree of vision.

The two following cases of especial interest have recently been studied by us:

CASE 1.—*Skeletal findings typical of arachnodactyly. Acute rheumatic fever. Rheumatic heart disease with mitral insufficiency.*

F. K., a 12 year old boy, was admitted to the medical service of the Johns Hopkins Hospital in September 1936, complaining of articular pains and epigastric discomfort. His mother, an emigrant from Ukraine, had died at the age of 37 of a renal disorder. It was reported that she had long fingers and toes, a hunched back and normal eyesight. The patient's father and one brother were normal. At birth the patient was noted to have long fingers and toes. At the age of 2½ years he was brought to the pediatric dispensary with Sydenham's chorea and was described as tall and undernourished. There was lateral curvature of the spine but no thoracic deformity. The heart was enlarged to the left, with a precordial systolic murmur loudest at the apex. The boy survived the chorea and two subsequent attacks of pneumonia but continued to be frail and suffered frequently from otitis media. He was able to maintain a creditable standing at a rural school but was clumsy and not proficient at sports. There was no complaint of dyspnea or cyanosis, and vision was normal. He was admitted to the hospital at the age of 12 in his second attack of polyarthritis in three years.

11. Börger, F.: Ueber zwei Fälle von Arachnodaktylie, Ztschr. f. Kinderh. **12**:161-184, 1915.

12. Dr. Rambar has given us permission to include this case in our series.

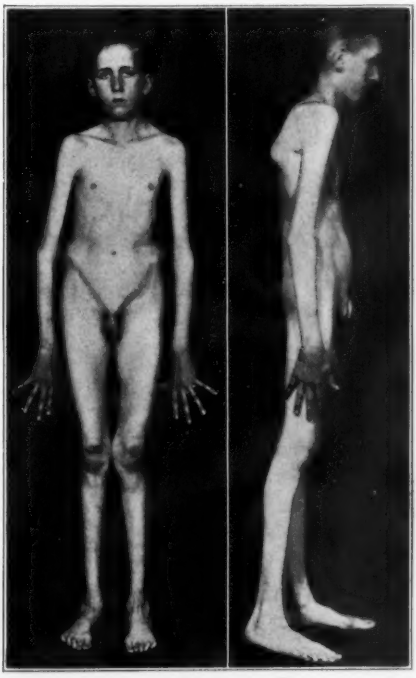

Fig. 1 (case 1).—Patient with arachnodactyly.

Fig. 2 (case 1).—Feet of a patient with arachnodactyly.

On admission to the hospital he had obvious acute rheumatic fever, with a temperature of 101.2 F., a pulse rate of 132 and typical subcutaneous rheumatic nodules over the knees and elbows. He was tall, gaunt and emaciated (height, 63¾ inches [162 cm.]; weight, 71 pounds [32 Kg.]). The fingers and toes were extraordinarily long, slender and slightly webbed. There was marked thoracic scoliosis to the right, with flattening of the right anterior portion of the chest and depression of the sternum. He walked awkwardly with inturned toes; there were bilateral pes planus and hallux valgus. The musculature was poorly developed but without evidence of amyotonia. The patellar ligaments were lax. The boy was dolichocephalic, with a long face and projecting ears.

Examination of the eyes by Dr. E. Burch revealed no abnormality other than a slight refractive error.

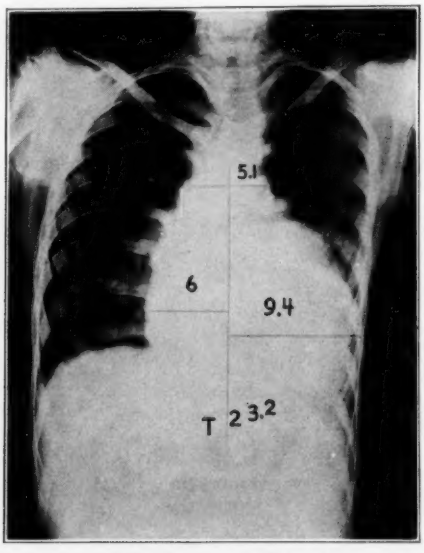

Fig. 3 (case 1).—Teleroentgenogram of a patient with arachnodactyly.

The heart was greatly enlarged, with the apical impulse in the posterior axillary line. The first sound at the apex was loud, and the second pulmonic sound was accentuated. There was a marked apical systolic thrill, and the accompanying murmur, though audible all over the precordium, was most loud and rough at the apex. Diastole was everywhere clear. The heart shifted well with a change of the patient's position.

The abdomen was not remarkable, the testes were in place in the scrotum and neurologic examination showed nothing abnormal.

The urinalysis and blood counts were normal save for mild anemia; the Wassermann reaction of the blood was negative. The calcium content of the serum was 10.2 mg. per hundred cubic centimeters. The basal metabolic rate was +20 per cent.

In the electrocardiogram the P wave was large, and in lead III it was biphasic.

Roentgenograms showed that the sella turcica was slightly smaller than normal. The cardiac measurements were valueless because of thoracic scoliosis,

but there was definite prominence in the region of the pulmonary conus and left auricle. The extremities were normal save for the unusual length and slimness of the phalanges, metacarpals and metatarsals.

After rest in bed and treatment with acetylsalicylic acid and digitalis the attack of rheumatic fever subsided, and the patient returned to school in four months. He returned to the hospital in August 1937 in myocardial failure and died. Permission for autopsy was not obtained.

CASE 2.—*Typical skeletal evidence of arachnodactyly. Pyopneumothorax.*

D. K., a 13 year old girl, entered the hospital in March 1936, complaining of pain in the right side of the chest. The family was of German descent. The parents and a younger brother were normal, but a first cousin on the maternal side had unusually long mobile fingers and had had two attacks of rheumatic fever,

Fig. 4 (case 2).—Showing the hypermobility of the joints in arachnodactyly.

without evidence of cardiac involvement. At birth the patient was noted to have long fingers and toes and a pigeon breast; later scoliosis developed. She was always thin and underweight, but her health otherwise was excellent. She was active and enjoyed sports, capitalizing her double-jointedness for the amusement of her friends. Her school record was excellent. There were no ocular or cardiac complaints. Four weeks previous to her admission to the hospital pneumonia developed, and when the fever did not subside after eleven days, the physician tapped the right side of the chest. While the needle was still in place, she experienced sharp pain and became short of breath. She continued to have fever and pain in the right side of the chest.

On admission to the hospital she appeared acutely ill, pale and undernourished. There were a spiking fever and typical signs of hydropneumothorax on the right. She was exceedingly thin, weighing only 71½ pounds (32.5 Kg.) and being 60 inches (152.5 cm.) tall, and had little subcutaneous fat. The extremities were

long and gracile, and the spidery fingers and toes presented an extraordinary appearance. There was remarkable hypermobility of all the joints, enabling her to perform such double-jointed feats as laying the shaft of the thumb flat along the radius with the wrist either flexed or extended. The skull was dolichocephalic, and the ears were prominent.

Examination of the eyes by Dr. E. Burch showed that they were essentially normal.

There were mild dorsal scoliosis to the left and pronounced pigeon breast. The heart was displaced to the left but otherwise normal. Secondary sexual characteristics were just beginning to develop.

The urinalysis and blood count were normal save for mild anemia and moderate leukocytosis associated with the infection. The Wassermann reaction of the blood was negative. Hydropneumothorax on the right was demonstrated roentgenographically, with loculation of the fluid; the heart appeared normal. Culture of the fluid aspirated from the chest showed Haemophilus influenzae and later Bacillus coli communis.

After a prolonged febrile course, rib resection was performed, and the child was discharged in good health after three and a half months in the hospital.

COMMENT

These reports are of interest not only because they exemplify arachnodactyly without ectopia lentis but because they describe instances of two medical conditions the association of which with arachnodactyly is perhaps of some significance. The first child had such obvious evidence of rheumatic infection elsewhere that the cardiac signs were attributed to mitral insufficiency, with possible early stenosis, even though underlying congenital heart disease was possible. It is interesting that three of Burch's eight patients were said to have had rheumatism. In one case a diagnosis of chronic adhesive pericarditis was made; in another there was a history of accentuation of cardiac symptoms after an attack of chorea, with the physical signs of mitral stenosis and aortic insufficiency, and in the third the physical signs of a double valvular lesion were present. In addition, the cousin of our second patient, who had stigmas of arachnodactyly, had had rheumatic fever in the past. Roesler,[13] in his review of hearts which showed as the chief congenital defect an interauricular septal defect greater than 1 cm., found that in 77.4 per cent there was also chronic valvular disease, probably of rheumatic origin. Since patency of the interauricular septum is the commonest cardiac anomaly in arachnodactyly, an increased incidence of rheumatic fever in these cases becomes possible. However, the problem of the differential diagnosis between congenital cardiac anomalies and possible superimposed rheumatic endocarditis is of course so difficult that without a considerable series of autopsies no definite conclusions can be reached.

13. Roesler, H.: Interatrial Septal Defect, Arch. Int. Med. **54**:339-380 (Sept.) 1934.

The second child, with pyopneumothorax, may be considered as demonstrating the well substantiated proclivity to pulmonary disorders shown by patients with Marfan's syndrome. The susceptibility of these patients to pneumonia is constantly referred to in the literature. The thoracic deformities, the anomalies in the arrangement of the lobes and the general frailty of these patients are usually given in explanation. It seems logical that these characteristics should tend to make the disease more grave and its complications more frequent.

SUMMARY

Two cases of arachnodactyly are reported with associated intrathoracic disease, in the first case rheumatic endocarditis being present and in the second case pyopneumothorax. The frequency of pneumonia in association with this syndrome is emphasized, and it is remarked that a number of the patients have had rheumatic fever. The characteristics of arachnodactyly from a general medical standpoint are reviewed, and it is pointed out that the better known ophthalmologic complications occur only in about half the cases and are not necessary for the diagnosis.

THE HEART IN ACROMEGALY

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The striking alterations of the skeletal, muscular, dermal and nervous systems produced by a chromophilic adenoma of the pituitary body have been adequately described by many observers. The changes produced in the cardiovascular system of patients with acromegaly, although the direct cause of death in the majority of instances, have been infrequently described and insufficiently studied. We have been impressed by the frequency with which weakness, syncope and the more common symptoms of cardiac failure have dominated the terminal clinical course in these cases. This circumstance has often been neglected because attention has been fixed on the more spectacular features of the disease, especially the surgical aspects. On this account, recent medical reports usually fail to describe adequately the changes in the cardiovascular system. We have had occasion to study a small number of patients with acromegaly with reference to the cardiovascular system both during life and at postmortem examination, and the results of these observations are embodied in this report.

The cause of the death of a patient with acromegaly, in the absence of intracranial complications, diabetes mellitus or a surgical procedure, is a subject of considerable interest. The progressive enfeeblement of the musculature and the ultimate onset of shortness of breath on the least exertion are in striking contrast to the appearance of great physical strength presented by these patients. This strange contrast was mentioned by Carlyle in his work entitled "History of Frederick the Great" and is known to all those who have watched the progress of the disease when unmodified by surgical or roentgen treatment.

Huchard,[1] in 1895, reported his studies of three acromegalic patients, with autopsy records. He stated that cardiomegaly might be part of general splanchnomegaly, it might be dependent on general arteriosclerosis

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Presented in abstract before the Association of American Physicians, May 5, 1936.

1. Huchard, H.: Anatomie pathologique, lésions et troubles cardio-vasculaires de l'acromégalie, J. d. praticiens **9**:249, 1895.

or it might be caused by deformity of the spine and of the thoracic cage. He submitted his theories to Pierre Marie, who suggested that in acromegaly there might be great hypertrophy of the whole cardiovascular system and also hypertrophy of the elements of the sympathetic nervous system.

The best and earliest collected review was published by Fournier,[2] in 1896. He studied twenty-five collected records and called particular attention to the clinical picture of heart failure in these cases. He emphasized the importance of easy fatigability, leading to extreme asthenia, combined with periods of syncope which often preceded the appearance of symptoms of grave heart failure. These symptoms were often associated with cardiomegaly and general splanchnomegaly, with the characteristic kyphotic deformity of the chest, with the high position of the heart and with variable degrees of arteriosclerosis.

Paviot and Beutter,[3] in 1904, described the large heart and the hypertrophy of the individual muscle fibers of an acromegalic patient who died of heart failure. Labadie-Lagrave and Deguy[4] and Alessandri[5] published records of two acromegalic patients with large hearts. One of these patients had hypertension, and the other had a saturnine nephropathy. Humphry and Dixon,[6] in 1910, studied an acromegalic patient with a large heart, marked splanchnomegaly and heart failure associated with moderate hypertension. They said they believed that they found a pressor substance in the urine. The heart at autopsy weighed nearly 1,300 Gm. Lubarsch,[7] in 1912, and Grellier,[8] in 1914, discussed this phase of acromegaly in brief articles. Amsler,[9] in 1912, discussed the theories of splanchnomegaly in acromegaly and concluded that the cardiac hypertrophy was hormonal in origin rather than secondary to certain other features of the disease, such as arterial hypertrophy,

2. Fournier, J. B. C.: Acromégalie et troubles cardio-vasculaires, Thesis, Paris, no. 111, 1896.

3. Paviot, J., and Beutter, M.: Acromégalie; splanchnomégalie; gros coeur; mort par asystolie, Lyon méd. **36**:1088, 1904.

4. Labadie-Lagrave and Deguy: Associations morbides de l'acromégalie, Arch. gén. de méd. **1**:129, 1899.

5. Alessandri, G.: Acromegalia con polso raro permanente ed enorme ipertensione arteriosa, Policlinico (sez. prat.) **15**:913, 1908.

6. Humphry, L., and Dixon, W. E.: A Case of Acromegaly with Hypertrophied Heart: Pressor Substances in the Urine, Brit. M. J. **2**:1047, 1910.

7. Lubarsch, O.: Hypophyse und Akro- und Splanchnomegalie, Jahresk. f. ärztl. Fortbild. **3**:70, 1912.

8. Grellier, G.: L'appareil circulatoire au cours de l'acromégalie, Thesis, Paris, no. 441, 1914.

9. Amsler, C.: Zur Lehre der Splanchnomegalie bei Akromegalie, Berl. klin. Wchnschr. **2**:1600, 1912.

kyphosis and splanchnomegaly. Eltester and Schroeder,[10] in 1914, discussed the problem of splanchnomegaly and reviewed the cardiovascular symptoms in acromegaly. Bassoe[11] stated that in acromegaly there is general dilatation of the blood vessels, with sclerosis and adrenal hyperplasia, and that a pressor substance is present in the blood. He said he believed that these factors are of prime importance in the production of cardiac hypertrophy.

A few of the monographs dealing with acromegaly have discussed the alterations of the cardiovascular system. Sternberg[12] stated that splanchnomegaly undoubtedly belongs to the phenomena of the disease:

> By certain authors (Klebs, Dallemagne, Huchard) the increase of the size of the heart so frequently observed is considered as belonging to it. The vessels, especially the arteries, are, as a rule, dilated and thickened. The thickening affects all three coats. True atheromatous changes may exist or may be altogether absent. The changes in the vessels extend from the aorta and pulmonary artery up to the fine ramifications in the organs as already described in connection with the skin. Examination of the thickened vessels shows increase of the endothelium of the intima, decrease of the musculature and compensation by the cellular tissue, and increase of the adventitia. According to Klebs, the dilatation is the primary, the active phase of the process, and the cellular tissue hyperplasia of the intima, with the consequent narrowing of the vessels, a secondary occurrence. Much may be said for the opposite opinion, that the dilatation is the secondary process, a result of the atrophy of the muscular and elastic tissue, and of their replacement by new-formed cellular tissue. The heart is, as a rule, enlarged—atrophy is described only by Henrot—especially dilatation and hypertrophy of the left ventricle. As in almost all cases, disease of the vessels just described was present, the changes in the heart may be, without difficulty, conceived as a natural result. Virga, Sigurini and Caporiacco have seen congenital narrowness of the aorta.

Sternberg also described the changes in the skin as follows:

> The small vessels at once attract notice owing to the thickness of their walls and dilatation. . . . The enlargement and affection of the heart may be, according to Huchard, accounted for in three ways: (1) by the splanchnomegaly; (2) by the arterial sclerosis; (3) by the alteration in shape of the cavity of the chest. Very frequently the sufferers show signs of insufficient cardiac action. The colour of the face is more or less cyanotic; a certain amount of dyspnoea is always suffered from. The general feebleness of the body, which is seldom wanting as the disease advances, is partly of cardiac action. Fainting fits are frequent. The disturbance of the circulation may be the most prominent condition in the disease, the patient becoming more and more dyspnoeic, finally oedematous, at last confined to his bed, and sinks from cardiac failure.

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10. Eltester and Schroeder: Ueber einen Fall von Akromegalie und Splanchnomegalie, Med. Klin. **10**:1311, 1914.

11. Bassoe, P.: Acromegaly, in Endocrinology and Metabolism, New York, D. Appleton & Company, 1922, vol. 1, p. 805.

12. Sternberg, M.: Acromegaly, translated by F. R. B. Atkinson, London, H. K. Lewis, 1899.

Marie and Souza-Leite [13] stated:

With regard to the vascular system, important changes have been noted. The heart is increased in size. This hypertrophy was more marked in Freund's case than in that of Erb, in whose patient a systolic bruit was heard at the apex.

Hinsdale [14] also discussed the subject. He stated:

The lesions of the vascular system present three phases—dilatation of the vessels, thickening of the walls, and obliteration of their lumen. In the first instance, there is a simple cardiomegaly, accompanied exceptionally with insufficiency of the cardiac valves. In the second, there is a true sclerotic myocarditis, a cardiorenal arteriosclerosis with what he (Fournier) terms a hyposystole, a cardiac liver with edema of the feet and albumen in the urine. Thus the heart participates in the general growth. In Osborne's case it weighed 39 ounces.

Cushing and Davidoff [15] reported the microscopic alterations of the heart of one of their patients as follows:

Histologically, the muscle fibers appear to be greatly enlarged and the supporting connective tissue markedly and diffusely increased. There are occasional scarred patches in which atrophic muscle fibers are seen. The larger blood vessels show some intimal thickening; the smaller ones are unaltered.

In this instance there was marked splanchnomegaly. The heart weighed 1,050 Gm. and presented concentric hypertrophy with little dilatation. This patient died of heart failure. These authors also discussed the heart in acromegaly as follows:

The largest recorded heart was also in Osborne's case, with the amazing weight of 1275 grams; the next largest was in our Case 1 of 1050 grams; the next in Case 3 of 1000 grams. These weights, needless to say, have been taken with the hearts emptied. Osborne's patient died of cardiac failure, just as did our Case 3, but this is not true of Case 1 which, of the two, had the larger heart. In Kraus's case, the heart weighed 950; in Widal's, 875; and in Paviot and Beutter's, 830 grams; the only other examples exceeding 500 grams. Several writers have been particularly struck by the absence of valvular disease or arteriosclerosis to which the huge hearts sometimes seen in acromegalics might be ascribed.

It is apparent that many theories may be formulated to explain the cardiac hypertrophy and eventual cardiac failure in this disease. A few of these may be profitably discussed at this point:

1. In the majority of these cases of cardiac hypertrophy and splanchnomegaly the size of the heart is out of proportion to the size

13. Marie, P., and Souza-Leite: Essays on Acromegaly, London, Adlard & Son, 1891.

14. Hinsdale, G.: Acromegaly, Detroit, W. W. Warren, 1898.

15. Cushing, H., and Davidoff, L. M.: The Pathological Findings in Four Autopsied Cases of Acromegaly, with a Discussion of Their Significance, Monograph 22, Rockefeller Institute for Medical Research, 1927.

of the patient or to his muscular development. It is necessary therefore to explain the cardiac hypertrophy by some other mechanism than general overgrowth of the individual with acromegaly, and, in addition, it is desirable to demonstrate that the hypertrophy is a "work hypertrophy." In the absence of hypertension, pericardial disease, marked arteriosclerosis, valvular disease, an increased basal metabolic rate or histologic evidences of progressive myocardial disease, no theory based on so-called work hypertrophy due to these particular causes can be sustained.

2. The cardiac hypertrophy in acromegaly is not causally related to an increased intracranial pressure, to diabetes mellitus or to an increased basal metabolic rate.

3. Although comparable statistics are not available, one can assume with reasonable certainty that the cardiac failure in acromegaly does not follow the general age curve of heart failure with advancing age. We believe that it is probably more directly related to the duration and the severity of the acromegalic process.

4. We are not of the opinion that the characteristic deformity of the chest, with displacement of the heart upward, plays any but a minor role in producing the cardiac hypertrophy and failure.

5. A review of the protocols of our cases clearly demonstrates that the causal factor did not originally lie in the heart itself. We have reviewed the sections of cardiac muscle from acromegalic patients who died of heart failure and from a series of patients with cardiac hypertrophy due to other causes, excluding obvious disease of the coronary artery. There is no constant histologic alteration present in the myocardium which distinguishes the enlarged acromegalic heart from other enlarged hearts. The factors we noted were fragmentation, fibrosis, cellular infiltration, the size of the muscle fibers and arteriosclerosis. Photomicrographs of these sections at a constant magnification have been studied with considerable care. No constant change could be found which would allow us to state which was and which was not the heart of a patient with acromegaly. Hypertrophy of the muscle fibers, which has been stated to be the cause of cardiomegaly in acromegaly, is not a constant finding; as a matter of fact, the largest, as well as the smallest, muscle fibers which we found were noted in the hearts of patients with acromegaly who had died of heart failure. When compared with muscle fibers of normal hearts or large hearts of patients without acromegaly, the muscle fibers of a large acromegalic heart may actually be smaller than normal. This fact only demonstrates again the absence of any correlation between the size of the muscle fiber of

the heart and its functional capacity. It may be assumed that hypertension, valvular heart disease and arteriosclerosis are not related in any way to the cardiac hypertrophy of acromegaly, in spite of the fact that in acromegaly the blood vessels are enlarged, both as to the thickness of the walls and as to the size of the lumens. It is our belief, therefore, that these factors are of little importance in the ultimate cardiac failure.

When all these factors are considered and given their proper significance, according to present knowledge, it may be concluded that in acromegaly, as in other types of cardiac enlargement, the hypertrophy is dependent on an increased "work demand" on the heart. It is probable that cardiac hypertrophy occurs first to compensate for the abnormal growth of the patient and to meet the increased demands occasioned by the general splanchnomegaly which is constantly present in acromegalic patients with heart failure. The abnormal growth of the patient, which is the important physiologic result of the hormonal disturbance produced by the eosinophilic adenoma, either directly or indirectly, leads to general muscular weakness and probably to cardiac muscular weakness. Thus the cardiac muscle, stimulated by hormonal influence to abnormal growth as regards either size or number of poorly functioning muscle cells, reaches the stage of diminishing cardiac reserve, which it attempts to meet by further hypertrophy. This hormonal theory in the present state of knowledge more nearly takes into account all the known circumstances and exceptions than any of the other theories which have been propounded.

An elevation of the basal metabolic rate has been observed in cases of eosinophilic adenoma of the pituitary body, first by Magnus-Levy [16] and subsequently by a large number of observers. It has been discussed by Davidoff,[17] Cushing and Davidoff [18] and Davis.[19] Anderson and Collip [20] have obtained an active thyrotropic substance from the anterior lobe of the pituitary body. It seems reasonable to assume that, in addition, an organotropic hormone must be present to produce the splanchnomegaly so frequently present in acromegaly. However, an elevated

16. Magnus-Levy, A.: Untersuchungen zur Schilddrüsenfrage, Ztschr. f. klin. Med. **33**:269, 1897.

17. Davidoff, L. M.: Studies in Acromegaly: The Anamnesis and Symptomatology in One Hundred Cases, Endocrinology **10**:461, 1926.

18. Cushing, H., and Davidoff, L. M.: Studies in Acromegaly: IV. The Basal Metabolism, Arch. Int. Med. **39**:673 (May) 1927.

19. Davis, A. C.: The Thyroid Gland in Acromegaly, Proc. Staff Meet., Mayo Clin. **9**:709, 1934.

20. Anderson, E. M., and Collip, J. B.: Thyreotropic Hormone of Anterior Pituitary, Proc. Soc. Exper. Biol. & Med. **30**:680, 1933.

basal metabolic rate is present in about 50 per cent of the cases of acromegaly. It is not a constant finding in cases of acromegaly with heart failure or in cases of acromegaly with marked splanchnomegaly. It should also be stated that the elevated metabolic rate is not always satisfactorily reduced by thyroidectomy or by iodine therapy.

We are inclined to believe that in the period of overactivity of the anterior lobe, the basal metabolic rate may be increased, but whether this is due to the hormone of the pituitary body, to the increased splanchnomegaly produced by this hormone or to some influence on the thyroid gland is not known. It is apparent that this manifestation of the disease needs further statistical study for its complete elucidation. We feel certain that the increased basal metabolic rate is of minor and probably negligible importance in the ultimate production of heart failure.

We have had the opportunity to study twenty-four patients with acromegaly for periods varying from a few months to over ten years. At the Los Angeles County Hospital there has been about one acromegalic patient for every ten thousand patients admitted. Of these twenty-four patients, ten were women. The ages varied from 25 to 60 years, the average being 48 years. The average age at death of those who died of heart failure was 48 years. The average age at the time of observation of all who had definite heart failure was 48 years. Of the twenty-four patients, eighteen had definite evidence of heart failure, and of this group, six have died of heart failure. At autopsy the hearts of these patients weighed 500, 400, 1,140, 1,200, 840 and 500 Gm., respectively. Three other patients of the entire group have died as a result of hemorrhage into the pituitary adenoma (heart weight, 500 Gm.), diabetic coma (heart weight, 280 Gm.) and psittacosis (heart weight, 540 Gm.), respectively. The basal metabolic rates for the group were not determined as a routine. One patient in early diabetic acidosis had a rate of + 27 per cent. One patient without cardiac symptoms had a rate of — 18 per cent. The rates for ten patients with varying degrees of heart failure were — 12, + 19, — 9, — 12, — 18, + 7, + 14, + 18, + 28 and — 1 per cent, respectively. A discussion of the significance of alterations of the basal metabolic rate may be found in the articles by Cushing and Davidoff [18] and Davis.[19]

There have been reported a number of instances of acromegaly and high blood pressure. Whether there is any causal relation between the two seems doubtful. In one of the patients in this group, a patient aged 50 with severe diabetes, hypertension developed during observation, and death resulted from heart failure. Another, aged 57, who died of cardiac failure, had a blood pressure of 150 systolic and 100

diastolic. Another, aged 56, had a pressure of 170 systolic and 90 diastolic. For the remainder the blood pressure was normal or slightly below normal.

Roentgenograms of the sella, the fingers and the heart, as well as perimetric observations, were made in nearly every instance and did not differ from those reported by other observers. It is of some interest that in this group of patients, none of whom had had any surgical procedure directed toward the pituitary adenoma, there was no instance of serious loss of useful vision.

The manifestations of disease presented by patients with acromegaly are so varied that they will not be discussed in their entirety at this time. We shall limit our remarks to those features of the disease which are associated in general with cardiac weakness and ultimate cardiac failure.

Weights, in Grams

Case	Heart	Lungs	Liver	Spleen	Kidneys	Thyroid	Brain
1	500	1,640	3,060	240	580	60	1,460
2	840	.....	2,820	480	...	660	.....
3	2 times normal	.....	Large	3 times normal	...	...	.....
4	1,200	.....	2,650	265	675	...	1,340
5	280	.....	2,900	260	...	...	.....
6	1,140	3,890	4,150	450	740	...	.....
7	400	.....	1,900	430	380	...	.....
8	540	.....	2,200	300	560	...	.....

It is well known that progressive weakness ultimately appears in patients with acromegaly if the active phase of the disease is sufficiently prolonged. In a few, after reaching a certain degree of intensity, the acromegalic features cease progressing, and the disease becomes quiescent. In a certain proportion of patients diabetes mellitus makes its appearance, and the patient may eventually die in diabetic coma. In the majority of all patients with acromegaly, symptoms referable to the heart eventually become the most striking clinical phenomena. In not a few cases the acromegalic changes may be meager, and the patient presents himself on account of headache, palpitation and breathlessness on exertion.

One of our patients had a basal metabolic rate of + 18 per cent. The heart was large, and he complained of headache and breathlessness. Thyroidectomy had been advised. However, on careful study it was found that he had no apparent abnormality of the thyroid gland but that he did have a large liver and a large spleen. Roentgenographic examination of the fingers and sella and perimetric studies of the visual fields confirmed the diagnosis of acromegaly. It is certain in this

instance that the splanchnomegaly preceded the development of the more usual acromegalic changes, and instances of this sort confirm our belief that the hormonal action on the heart is the primary factor in the ultimate production of heart failure, not the skeletal, muscular, dermal or vascular overgrowth. This patient was treated vigorously with roentgen rays, and the splanchnomegaly and the symptoms of heart failure disappeared.

A second patient presented himself on account of an unproductive cough. On examination the lungs appeared normal, but the heart, liver and spleen were enlarged. No cause for the cardiac enlargement could be determined. The patient showed few of the usual symptoms of acromegaly, but examination of the bones and of the sella roentgenographically showed the characteristic changes of acromegaly. The cough was probably dependent on enlargement of the larynx. The shortness of breath on exertion, of which he complained, was greatly relieved by roentgen therapy.

In general, the first symptom complained of by these patients is weakness. This weakness, of course, is in striking contrast to the great muscular development. As the symptoms increase, the weakness and easy fatigability are augmented by palpitation and breathlessness on exertion. Soon attacks of syncope make their appearance, and the patient becomes practically an invalid. As the disease progresses a striking pallor appears, asthenia becomes extreme, breathlessness becomes constant, the pulse becomes rapid and irregular and the patient succumbs to heart failure.

A few individual symptoms and signs may now be discussed. 1. Hypertension is not a feature of acromegaly and in our opinion is not produced by acromegaly. When present it should be looked on as a coincidental disease. 2. Valvular disease of the heart when present in patients with acromegaly is also probably due to some other disease. 3. Hypertrophy of the heart is always present in patients with acromegaly and heart failure. The heart may be of enormous size. In one of our cases the heart weighed 1,200 Gm. 4. The electrocardiographic changes are neither constant nor specific. There is usually evidence of left axis deviation, and as the disease progresses, changes of the QRS complex, usually with broadening and slurring and at times notching and widening, point to disturbances of impulse conduction due to diffuse myocardial damage. Later, various arrhythmias may make their appearance, and in the later stages significant changes of the T wave may appear.

In the terminal stages of the disease the symptoms of heart failure differ little from those seen in other types of heart failure. The rapid or irregular pulse can no longer be slowed with moderate doses of digi-

talis, breathlessness and orthopnea become marked, cyanosis is striking, edema, pulmonary congestion and Cheyne-Stokes respiration appear and the patient ultimately dies of heart failure.

SUMMARY

This report is based on the observations of twenty-four patients with acromegaly. Of this group, eighteen (75 per cent) presented evidence of marked heart failure, and six have died of heart failure. These six patients all had marked splanchnomegaly and cardiomegaly, and an eosinophilic pituitary adenoma was observed post mortem.

CHOLESTEROL CONTENT OF THE BLOOD IN HEART DISEASE

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To the steadily increasing number of studies of cholesterol in the blood in various clinical entities reported in the literature, we now add our investigation on the concentration of this lipid in the blood in heart disease.

MATERIAL AND METHODS

The subjects used in this study were chosen at random from the group of patients who had been attending the cardiac clinic for adults of the New York Post-Graduate Hospital for at least one year and for whom the etiologic diagnosis was reasonably certain. When the conditions were classified functionally according to the standards of the New York Heart Association, the cases fell, for the most part, into classes 2a and 2b, with an occasional case belonging to either class 3 or class 1. A total number of sixty-one patients were studied, eighteen of whom had rheumatic heart disease, twenty-four had arteriosclerotic heart disease and nineteen had hypertensive heart disease; the patients with hypertension also manifested some evidence of arteriosclerosis. A group of thirty-three normal subjects was used for comparative study.[1]

Only single studies of the blood were carried out, venipuncture being done between 2 and 3 p. m. No attempt was made to determine the amount or type of food previously consumed, since it has been shown that the ingestion of food does not alter appreciably the cholesterol content of the blood.[2] The total cholesterol and ester cholesterol contents were determined for the plasma by the Bloor-Knudson[3] procedure, modified with temperature control as practiced in this laboratory.[4]

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1. The normal subjects had been studied in this laboratory by means of the same analytic procedures used in the present investigation (Hartung, E. F., and Bruger, M.: The Cholesterol Content of the Plasma in Arthritis, J. Lab. & Clin. Med. **20**:675, 1935).

2. Bruger, M., and Somach, I.: The Diurnal Variations of the Cholesterol Content of the Blood, J. Biol. Chem. **97**:23, 1932.

3. Bloor, W. R., and Knudson, A.: The Separate Determination of Cholesterol and Cholesterol Esters in Small Amounts of Blood, J. Biol. Chem. **27**:107, 1916.

4. Mirsky, I. A., and Bruger, M.: A Note on the Liebermann-Burchard Color Reaction for Cholesterol, J. Lab. & Clin. Med. **18**:304, 1932.

RESULTS

In order to conserve space the individual results will not be detailed. As shown in the accompanying chart, the patients with rheumatic heart disease tended to have a lower concentration of cholesterol in the blood than those with either arteriosclerotic or hypertensive heart disease. Thus, it will be observed that whereas 28 per cent of the patients with rheumatic heart disease had blood cholesterol values below 150 mg. per hundred cubic centimeters, not one of the patients with either arteriosclerotic or hypertensive heart disease exhibited a similar hypocholesteremia. Again, it will be noted that whereas only 5 per cent of the

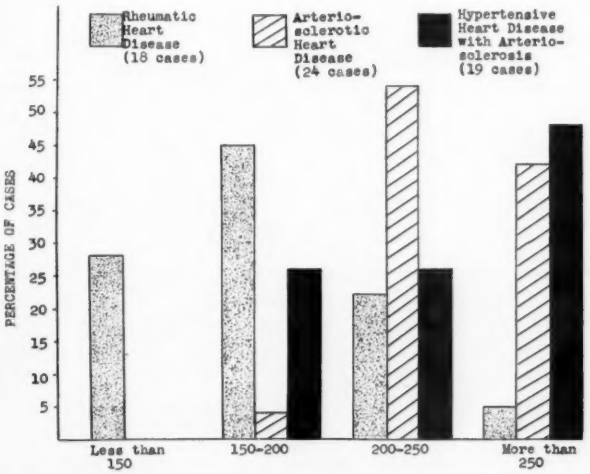

Chart showing the frequency distribution for total plasma cholesterol for patients with heart disease.

patients with rheumatic heart disease showed a concentration of cholesterol in the blood over 250 mg. per hundred cubic centimeters, approximately 45 per cent of the patients with either arteriosclerotic or hypertensive heart disease demonstrated this hypercholesteremia. Although a noteworthy difference as to the concentration of the cholesterol in the blood existed between patients with rheumatic heart disease, on the one hand, and those with arteriosclerotic or hypertensive heart disease, on the other, little or no difference could be observed as to the distribution of the blood cholesterol values when the patients with arteriosclerotic and those with hypertensive heart disease were compared.

The results are treated statistically in the accompanying table. The arithmetical means indicate the trend; the cholesterol content of the plasma tended to be low in rheumatic heart disease and elevated in arteriosclerotic or hypertensive heart disease. The results for the group with rheumatic heart disease were not significant on a statistical basis, since the difference between the means for the group of normal subjects and those for the group with rheumatic heart disease divided by the standard error of the difference of these means gave a value of only 1.03. However, when the same calculations were employed for the groups of patients with arteriosclerotic and with hypertensive heart disease, the results were 4.9 and 4.29, respectively, values that are statistically significant.

The Total Cholesterol Content of the Plasma of Normal Subjects and of Patients with Heart Disease: Statistical Analysis

Group	Number of Observations	Arithmetical Mean, Mg. per 100 Cc.	Standard Deviation*	Probable Error of Mean†	$\frac{d}{\sigma D}$‡
Normal	33	195	29	3.42	
Rheumatic heart disease	18	185	35	5.56	1.03
Arteriosclerotic heart disease	24	248	47	6.48	4.90
Hypertensive heart disease with arteriosclerosis	19	246	47	7.27	4.29

* Standard deviation $\sigma = \sqrt{\frac{\Sigma (d^2)}{N}}$. $\Sigma (d^2)$ represents the summation of the squares of the individual deviations from the mean and N the number of determinations.

† Probable error of mean $= 0.6745 \frac{\sigma}{\sqrt{N}}$. σ represents the standard deviation and N the number of determinations.

‡ $\frac{d}{\sigma D}$ represents the difference between two means divided by the standard error of the difference. The standard error of the difference, σD, is calculated from the formula $\sigma D = \sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}}$. σ_1 and σ_2 represent the standard deviations for the two groups, and N_1 and N_2 represent the number of determinations for the two groups.

No appreciable difference was observed in the ratios of ester to free cholesterol in the three major types of heart disease considered. For patients with rheumatic heart disease the average ester-free ratio was 1.7; for those with arteriosclerotic heart disease, 1.86, and for those with hypertensive heart disease, 1.77.

COMMENT

It is generally known that patients with rheumatic heart disease fall into a decidedly lower age group than those with either arteriosclerotic or hypertensive heart disease, and it may be inferred that the observed differences in the cholesterol content of the blood in the various types of heart disease may be due to the age factor. Parhon and Parhon [5]

5. Parhon, C. J., and Parhon, M.: L'hypercholestérinémie de la viellesse, Compt. rend. Soc. de biol. **88**:231, 1923.

have maintained that there is a slight increase in the blood cholesterol content with advancing years in human beings; in persons over 70 years of age they frequently observed definite hypercholesteremia. However, Gorham and Myers [6] reported that the blood cholesterol values for fourteen normal subjects, 3 of whom were 51, 65 and 55 years old, respectively, ranged from 130 to 170 mg. per hundred cubic centimeters. In a recent detailed study on the plasma lipid content for normal men at different ages, Page and his associates [7] demonstrated that variations of age from 20 to 90 years do not have a determinable influence on either the amount or the composition of the plasma lipids. Differences in age distribution, therefore, apparently fail to account for the variations in the level of the blood cholesterol noted in the various types of heart disease considered.

A more probable explanation for the hypocholesteremia frequently observed in rheumatic heart disease is the presence of the underlying infectious process. The cholesterol content of the blood is consistently decreased in infectious diseases, especially in the acute febrile disorders [8] and in the acute stages of syphilis,[9] leprosy,[10] typhoid [11] and tuber-

6. Gorham, F. D., and Myers, V. C.: Remarks on the Cholesterol Content of Human Blood, Arch. Int. Med. **20**:599 (Oct.) 1917.

7. Page, I. H.; Kirk, E.; Lewis, W. H., Jr.; Thompson, W. R., and Van Slyke, D. D.: Plasma Lipids of Normal Men at Different Ages, J. Biol. Chem. **111**:613, 1935.

8. (*a*) Bacmeister and Henes, E.: Untersuchungen über den Cholesteringehalt des menschlichen Blutes bei verschiedenen inneren Erkrankungen, Deutsche med. Wchnschr. **39**:544, 1913. (*b*) Henes, E.: Untersuchungen über den Cholesteringehalt des menschlichen Blutes bei inneren Erkrankungen, Deutsches Arch. f. klin. Med. **111**:122, 1913. (*c*) Wacher, L., and Hueck, W.: Chemische und morphologische Untersuchungen über die Bedeutung des Cholesterins im Organismus, Arch. f. exper. Path. u. Pharmakol. **74**:416, 1913. (*d*) Kipp, H. A.: Variation in the Cholesterol Content of Serum in Pneumonia, J. Biol. Chem. **44**:215, 1920. (*e*) Denis, W.: Cholesterol in Human Blood Under Pathological Conditions, ibid. **29**:93, 1917. (*f*) Boyd, E. M.: The Lipopenia of Fever, Canad. M. A. J. **32**:500, 1935. (*g*) Stoesser, A. V., and McQuarrie, I.: Influence of Acute Infection and Artificial Fever on the Plasma Lipids, Am. J. Dis. Child. **49**:658 (March) 1935. (*h*) Stoesser, A. V.: Study of Cholesterol Fractions in Acute Infections of Infants With and Without Eczema, Proc. Soc. Exper. Biol. & Med. **34**:10, 1936.

9. Knudson, A.; Ordway, T., and Ferguson, H.: Cholesterol and Cholesterol Esters in Blood Showing a Positive Wassermann Reaction, Proc. Soc. Exper. Biol. & Med. **18**:299, 1921. Rosen, I., and Krasnow, F.: Blood Cholesterol Findings in Syphilis and Other Skin Diseases: An Accurate Technic for Extracting Blood Cholesterol, Arch. Dermat. & Syph. **13**:506 (April) 1926. Feraru, F., and Offenkrantz, F. M.: Serum Cholesterol in Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **21**:267, 1937.

10. Boyd, T. C., and Roy, A. C.: Notes on the Cholesterol Content of Indian Blood in Health and Leprosy, Indian J. M. Research **15**:643, 1928.

11. Chauffard, A.: Laroche, G., and Grigaut, A.: Évolution de la cholestérinémie chez les typhiques, Compt. rend. Soc. de biol. **70**:70, 1911.

culosis.[12] In rheumatoid arthritis, a disease presumably infectious in origin, the cholesterol content is also frequently diminished.[13] Kipp[8d] attempted to explain the low cholesterol value by assuming a greater utilization of this lipid in the body in the presence of infection.

Although reports of numerous studies on the cholesterol content of the blood in essential hypertension and arteriosclerosis have been published during the past twenty-five years, the results, even in recent years with improved methods, have not been uniform. In 1936 Page, Kirk, and Van Slyke,[14] and Elliot and Nuzum[15] reported that patients with essential hypertension with or without arteriosclerosis did not have an elevated cholesterol level. More recently, Davis, Stern and Lesnick[16] found the average cholesterol level to be higher for patients with angina pectoris of atherosclerotic origin than for a group of control subjects. Since Saphir and his co-workers[17] have observed that patients with coronary atherosclerosis always manifest generalized arteriosclerosis in the aorta and other vessels of the body, the results of Davis, Stern and Lesnick, as suggested by these writers, indicate that patients with generalized arteriosclerosis manifest a higher average cholesterol value than do normal subjects. Our findings in arteriosclerotic heart disease and in hypertensive heart disease with arteriosclerosis also demonstrate that the advent of vascular degeneration in man is frequently accompanied with an elevation of the cholesterol level of the blood.

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12. Bacmeister and Henes.[8a] Eichelberger, L., and McCluskey, K. L.: Chemical Studies in Tuberculosis: I. Plasma Proteins, Cholesterol and Corpuscle Volume, Arch. Int. Med. **40**:831 (Dec.) 1927. King, S. E., and Bruger, M.: Plasma Cholesterol in Tuberculosis and Amyloid Disease, Ann. Int. Med. **8**:1427, 1935.

13. Bruger, M., and Poindexter, C. A.: Relation of the Plasma Cholesterol to Obesity and to Some of the Complicating Degenerative Diseases (Diabetes Mellitus, Essential Hypertension, Osteo-Arthritis and Arteriosclerosis), Arch. Int. Med. **53**:423 (March) 1934. Hartung, E. F., and Bruger, M.: The Cholesterol Content of the Plasma in Arthritis, J. Lab. & Clin. Med. **20**:675, 1935.

14. Page, I. H.; Kirk, E., and Van Slyke, D. D.: Plasma Lipids in Essential Hypertension, J. Clin. Investigation **15**:109, 1936.

15. Elliot, A. H., and Nuzum, F. R.: Cholesterol Content of Whole Blood in Patients with Arterial Hypertension, Arch. Int. Med. **57**:63 (Jan.) 1936.

16. Davis, D.; Stern, B., and Lesnick, G.: The Lipid and Cholesterol Content of the Blood of Patients with Angina Pectoris and Arteriosclerosis, Ann. Int. Med. **11**:354, 1937.

17. Saphir, O.; Priest, W. S.; Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis, and the Resulting Myocardial Changes, Am. Heart J. **10**:762, 1935.

CONCLUSIONS

There is a marked difference between the cholesterol content of the plasma of patients with rheumatic heart disease and that of patients with arteriosclerotic or hypertensive heart disease. Patients with rheumatic heart disease frequently demonstrate hypocholesteremia, although for all the patients as a group, the results lack statistical significance when compared with the cholesterol content of the blood of normal subjects. In contrast is the hypercholesteremia often observed for patients with arteriosclerotic heart disease or hypertensive heart disease manifesting some evidence of arteriosclerosis; for these two groups, however, the increase in the plasma cholesterol value is of sufficient magnitude to be statistically significant. For the most part, there is little or no difference between the ratio of ester to free cholesterol in the three types of heart disease studied.

CLINICAL STUDIES OF RESPIRATION

VI. EXPIRATORY INFLATION DURING AIR HUNGER AND DYSPNEA PRODUCED BY PHYSICAL EXERTION IN NORMAL SUBJECTS AND IN PATIENTS WITH HEART DISEASE

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Extreme expiratory inflation was apparently of major importance in the production of air hunger and dyspnea in several of our patients with the effort syndrome. These observations suggested that enlargement of the expiratory volume of the chest might be a factor in the production of air hunger and dyspnea in patients with cardiac failure. In a previous study[1] the respirations were stimulated by reducing the oxygen or increasing the carbon dioxide content of the inspired air, both separately and simultaneously, and it was found that patients with cardiac failure were able to tolerate as great alterations of the inspired air as those tolerated by normal subjects. The former group, on the other hand, were unable to perform as much physical exercise as the normal subjects. These observations indicate that the respiratory stimulus produced by physical exertion is different from that produced by alteration of the inspired air. The purpose of the present study was to ascertain the effect of hyperpnea produced by physical exertion on the expiratory volume of the chest of normal subjects and of patients with heart disease.

METHOD

Plethysmograms were obtained by the method previously described.[2] The apparatus was arranged at the beginning of each experiment (fig. 1) and was

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1. Greene, J. A., and Heeren, R. H.: Clinical Studies of Respiration: V. Relation of Dyspnea and Air Hunger to Changes of the Expiratory Volume of the Chest, Arch. Int. Med. **57**:100 (Jan.) 1936.

2. Greene, J. A., and Coggeshall, H. C.: Clinical Studies of Respiration: I. Plethysmographic Study of Quiet Breathing and of the Influences of Some Ordinary Activities on the Expiratory Position of the Chest in Man, Arch. Int. Med. **52**:33 (July) 1933.

not altered during the period of observation. A control period was continued until the pulse rate and the arterial pressure, which were recorded at one minute intervals throughout the experiment, and the expiratory volume became constant. Physical exertion was obtained by having the subject pedal a stationary bicycle while he reclined in a chair. The duration of exertion varied, but it was continued until definite shortness of breath developed. The same degree of dyspnea was not produced in each instance. The distance traveled, which was measured by an odometer, also varied. Recovery from the exertion was considered complete after the pulse rate and the arterial pressure had reached the previous resting levels and the expiratory volume had become constant. Observations were continued in each experiment for at least ten minutes after recovery. Activity altered the

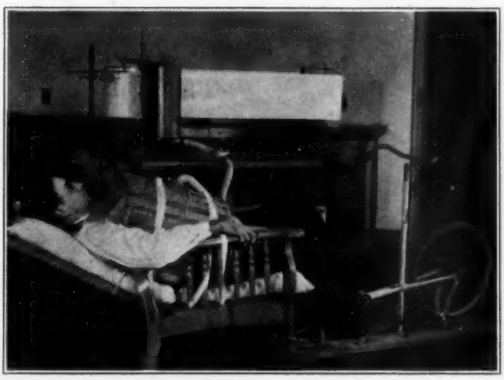

Fig. 1.—The subject is shown in a reclining position, with the plethysmograph in place, pedaling a bicycle.

relation of the subject to the plethysmographic bag; therefore, only records obtained during the period of recovery were studied.

The control group consisted of 12 normal medical students and physicians. Of the 17 patients studied, 3 had arthritis of the spine, 1 aplastic anemia, 1 allergic asthma and pulmonary emphysema and 12 organic heart disease. The last group included 3 without congestive failure and 6 with slight, 1 with moderate and 2 with advanced congestive failure.

RESULTS

The expiratory volume of the chest increased in all instances during hyperpnea produced by physical exertion. A typical example is shown in figure 2.

Three possible sources of error had to be excluded before these results could be accepted: first, the apparatus recorded the complete expirations during hyperpnea; second, muscular relaxation was complete

immediately after the occurrence of exertion, and, third, flexion or extension of the spine did not produce the results. The first possible source of error was excluded because forced expirations during hyperpnea were recorded (fig. 3). The second was difficult to eliminate, but

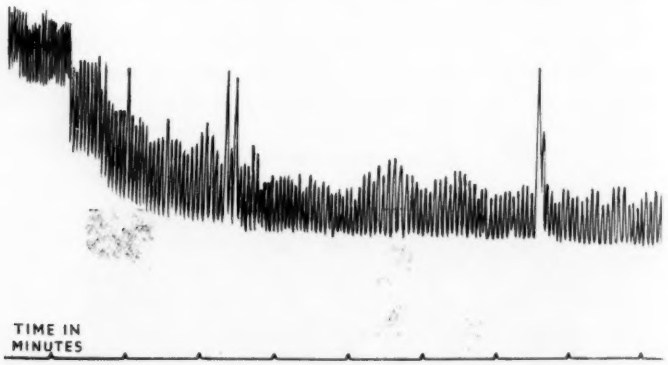

Fig. 2.—Plethysmogram taken during recovery from physical exertion, showing expiratory deflation.

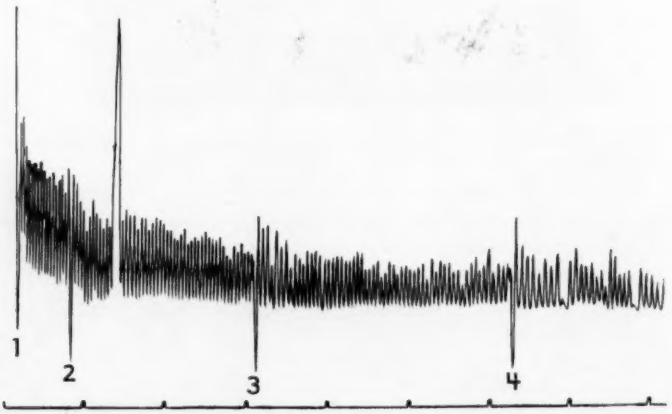

Fig. 3.—Plethysmogram taken during recovery from physical exertion. Forced expirations are recorded at *1, 2, 3* and *4*.

each person felt that muscular relaxation was complete as soon as the exertion ended. The third was excluded by the occurrence of alterations in the expiratory volume of the chest of patients with immobility of the spine due to arthritis.

Greater expiratory inflation occurred in patients with heart disease than in normal subjects. As graphically recorded, the inflations averaged 38.9 mm., as compared to 30.1 mm. It will be noted from table 1 that this phase also persisted longer in proportion to the distance recorded on the odometer in patients with cardiac disease.

TABLE 1.—*Comparison of the Duration of Expiratory Inflation and the Distance Traveled**

Subjects	Average Distance, Miles	Average Duration of Expiratory Inflation, Minutes
Normal subjects	2.9	6.6
Patients with heart disease	0.6	5.8
Others	0.9	4.9

* The expiratory inflation persisted longer in proportion to the distance traveled in patients with heart disease than in normal subjects.

TABLE 2.—*Comparative Data on the Duration of Expiratory Inflation, the Distance Traveled and the Severity of Congestive Heart Failure**

Degree of Heart Failure	Average Distance, Miles	Average Duration of Expiratory Inflation, Minutes
None	0.7	5.7
Slight	0.8	6.0
Moderate	0.4	6.0
Severe	0.2	5.5

* The more severe the congestive heart failure, the longer the expiratory inflation persisted in proportion to the amount of physical exertion.

TABLE 3.—*Comparative Data on the Pulse Rate, Arterial Pressure and Duration of Expiratory Inflation**

Subjects	Average Increase of Pulse Rate, Beats per Minute	Average Elevation of Arterial Pressure (Systolic) Mm. of Hg	Average Duration of Expiratory Inflation, Minutes
Normal	58	48	6.6
Patients with heart disease	29	20	5.8
Others	30	26	4.9

* Although there was a greater relative demand placed on the cardiocirculatory system of normal subjects, as shown by the increase in pulse rate and arterial pressure, the duration of the expiratory inflation was proportionately less than that for patients with heart disease.

The duration of altered thoracic volume was less in proportion to the degree of exertion for patients with heart disease without failure than for those with congestive failure (table 2).

The patients exerted themselves less vigorously than did the normal subjects, and a longer time was required to pedal the same distance; consequently, the duration of expiratory inflation was compared to the maximum increase of pulse rate and of arterial pressure. It will be noted from table 3 that the patients with heart disease had relatively less strain on the cardiocirculatory system, yet the expiratory inflation persisted proportionately longer than in the normal subjects. Two normal subjects, not included in the table, showed a persistent elevation of thoracic volume out of proportion to the distance traveled or to the relative strain on the cardiocirculatory system.

COMMENT

The occurrence of expiratory inflation during hyperpnea in all instances after physical exertion indicates that this is a normal response to hyperpnea thus produced. Our findings are in accord with those of Bohr [3] and Siebeck,[4] who observed an increase in the middle position of the chest after physical exertion.

The greater and proportionately longer expiratory inflation observed in our patients with heart disease could be attributed to an abnormal respiratory response to a given amount of physical exertion, as pointed out by Harrison, Harrison, Calhoun and Marsh.[5]

Expiratory enlargement of the chest decreases the effective vital capacity, which is already diminished in cases of cardiac failure, and is undoubtedly a contributory factor in the production of air hunger and dyspnea. In certain patients with effort syndrome, expiratory inflation became so marked that only small expirations were possible; consequently, the respirations became shallow and rapid. Such extreme expiratory enlargement was not observed in any patient with cardiac failure; therefore, it appears that this phenomenon is not as important in the production of air hunger and dyspnea in cases of heart failure as in effort syndrome.

SUMMARY

The expiratory volume of the chest has been studied during hyperpnea produced by physical exertion in normal subjects and in patients

3. Bohr, C.: Die funktionellen Aenderungen in der Mittellage und Vitalkapazität der Lungen, Deutsches Arch. f. klin. Med. **88**:385, 1906-1907.

4. Siebeck, R.: Ueber die Beeinflussung der Atemmechanik durch krankhafte Zustände des Respirations-und Kreislaufapparates, Deutsches Arch. f. klin. Med. **100**:204, 1910.

5. Harrison, T. R.; Harrison, W. G.; Calhoun, J. A., and Marsh, J. P.: Congestive Heart Failure: XVII. The Mechanism of Dyspnea on Exertion, Arch. Int. Med. **50**:690 (Nov.) 1932.

with heart disease. The increase observed in all instances was of greater degree and proportionately of longer duration in the patients. These results indicate that expiratory inflation per se is not the major factor in the production of air hunger and dyspnea in cases of cardiac failure.

DIRECT MEASUREMENT OF HEIGHT OF THYROID EPITHELIUM

A METHOD OF ASSAY OF THYROTROPIC SUBSTANCE; CLINICAL APPLICATION

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A convenient, specific and delicate method of assay of the thyrotropic principle of the anterior lobe of the pituitary body is required for physiologic and clinical studies. Various methods have been used. Loeb [1] and his associates, in 1928, described a quantitative method that had been used by them for several years, namely, the determination of the mitotic index. The entire thyroid gland of the test animal, the guinea pig, was cut in serial section and stained with hematoxylin and eosin. The average number of sections obtained for each gland varied between four hundred and fifty and five hundred; mitoses were counted in every tenth section in an exact manner; the number of mitoses thus obtained was multiplied by 10 to obtain the total number of mitoses in the gland. A marked increase in the number of mitoses occurs with thyroid hypertrophy.

Several workers have described the degrees of hyperplastic change resulting from the administration of increasing amounts of thyrotropic substance (Aron,[2] Loeser [3] and Severinghaus [4]). Junkmann and Schoeller [5] have given a more detailed description and have proposed

From the Department of Medicine, Northwestern University Medical School.

1. Loeb, L., cited by Rabinovitch, J.: The Effect of Feeding Potassium Iodide on the Proliferative Activity of the Thyroid Gland in Guinea Pigs, Am. J. Path. **4**:601-611, 1928.

2. Aron, M.: L'hormone préhypophysaire excito-sécrétrice de la thyroïde: Contribution à l'étude du fonctionnement thyroïdien, Rev franç. d'endocrinol. **8**: 472-520, 1930.

3. Loeser, A.: Die Darstellung thyreotropwirksamer Extrakte aus Hypophysenvorderlappen, Arch. f. exper. Path. u. Pharmakol. **166**:693-702, 1932.

4. Severinghaus, A. E.: Cytological Observations on the Secretion in Normal and Activated Thyroids, Ztschr. f. Zellforsch. u. mikr. Anat. **19**:653-680, 1933.

5. Junkmann, K., and Schoeller, W.: Ueber das thyreotrope Hormon des Hypophysenvorderlappens, Klin. Wchnschr. **11**:1176-1177, 1932.

a unit of thyrotropic activity in terms of the microscopic picture of hyperplasia. Collip [6] has defined a unit as "the minimum amount administered daily in two injections which will cause a rise of 20 per cent in the metabolism of the hypophysectomized rats by the fourth day." Cuyler, Stimmel and McCullagh [7] have resorted to determination of the total iodine content of the thyroid gland to measure thyrotropic activity. The iodine content decreases with stimulation. One unit was considered to be the amount which would decrease the iodine content to half the average normal content. The acceleration of the metamorphosis of tadpoles was also used by these authors to quantitate thyrotropic activity. Klein [8] suggested determining the average diameter of a hundred follicles—the follicular index—as a method of representing the degree of colloid storage in the gland. Hertz and Oastler [9] determined the presence of thyrotropic substance without measurement of the amount by the ability of the unknown material to prevent atrophy of the thyroid gland of the rat after hypophysectomy. Heyl and Laqueur [10] reviewed the problem of quantitative assay of thyrotropic substance, rejected the indirect methods based on metabolism and also the method based on the weight of the gland and returned to analyses of the visual impression of the hyperplastic changes, which occur chiefly in the center of the gland. They defined six stages. Recently Aron [11] reconsidered the problem and suggested that a unit of thyrotropic activity would be the amount producing a certain increase, for instance, of 5 to 10, in the number of mitoses per microscopic field in the thyroid gland of the guinea pig.

This problem was clearly stated in the important contribution by Rowlands and Parkes.[12] After considering the preceding methods they resorted to the common procedure of bioassay, namely, study of the

6. Collip, J. B., and Anderson, E. M.: The Production of Serum Inhibitory to the Thyrotropic Hormone, Lancet **1**:76-78, 1934.

7. Cuyler, W. K.; Stimmel, B. F., and McCullagh, D. R.: Quantitative Studies with Thyrotropic Hormone, J. Pharmacol. & Exper. Therap. **58**:286-293, 1936.

8. Klein, J.: The Correlation of Mineral Metabolism and the Vegetative Nervous System in Thyroid Disease, Ann. Int. Med. **8**:798-804, 1935.

9. Hertz, S., and Oastler, E. G.: Assay of Blood and Urine for Thyrotropic Hormone in Thyrotoxicosis and Myxedema, Endocrinology **20**:520-525, 1936.

10. Heyl, J. G., and Laqueur, E.: Zur quantitativen Bestimmung der thyreotropen Wirkung von Hypophysenvorderlappenpräparaten und die Einheit des thyreotropen Hormons, Arch. internat. de pharmacodyn. et de thérap. **49**:338-354, 1935.

11. Aron, M.: Sur le titrage biologique de la thyréostimuline préhypophysaire: Le "seuil des mitoses" dans la thyroide des cobayes traités, Compt. rend. Soc. de biol. **123**:250-253, 1936.

12. Rowlands, I. W., and Parkes, A. S.: Quantitative Study of the Thyrotropic Activity of Anterior Pituitary Extracts, Biochem. J. **282**:1829-1843, 1934.

increase in weight of the gland. They were able to show a characteristic curve of increase of weight accompanied by increasing dosage. They defined a unit as the thyrotropic activity contained in an amount of thyrotropic substance which when given daily for five days will cause the thyroid gland of immature guinea pigs to attain a weight of 60 mg. (i. e., a doubling of the weight). This weight was determined after fixation of the gland in Bouin's fluid and dehydration to the stage of preparation for sectioning at which 70 per cent alcohol is employed.

No comprehensive study comparing the advantages of these various procedures has been made, but in general it may be assumed that (1) the mitotic index of Loeb, while undoubtedly sensitive, objective and accurate, must be time consuming; (2) the descriptive histologic methods, depending on the visual impression of the individual observer, are not objectively accurate; (3) the metabolic studies of Collip and the thyroid maintenance plan of Hertz require hypophysectomy to render the rat sensitive to thyrotropic substance; Collip's method is indirect, depending on a secondary variable—the sensitivity of the test animal to the thyroid substance produced by its stimulated gland; the Hertz technic requires eight days of maintenance and subsequent comparison and is not quantitative; (4) the only objection to the unit of Rowlands and Parkes is that it may not be small enough (this is not a fundamental criticism of the unit but implies that the method is not a delicate one). For physiologic studies of the guinea pig a method for detecting levels of thyrotropic substance similar to those that are normal for the animal is required to learn the factors normally influencing thyroid physiology. In view of these objections we suggest the following method.

EXPERIMENTAL STUDIES

The actual measurement of the height of the thyroid epithelium may be used to estimate the hyperplasia produced by thyrotropic substance. This procedure is analagous to the Price-Jones[13] technic for studying red blood cells.

For test animals we use immature female guinea pigs which have been kept on a standard laboratory diet and which weigh from 180 to 225 Gm. The material to be tested is administered in three daily subcutaneous injections. The animal is killed with ether on the fourth day. The thyroid gland is removed on the trachea and fixed in solution of formaldehyde. Paraffin sections are made and stained with hematoxylin and eosin. The section is mounted so that the long axis of the gland is at right angles to the slide; this allows long parallel paths to be followed with the mechanical stage of the microscope. With the oil immersion lens (we use a Leitz echelon micrometer that is calibrated so that one division equals 0.75 microns) the height of the cell of average size in the wall of 200 successive distinct acini is measured. Interacinar cells are neglected.

13. Price-Jones, C.: Red Blood Cell Diameters, London, Oxford University Press, 1933.

Acini of all diameters are used but only if a distinct lumen is present. These 200 measurements are tabulated, and a graph is made of the frequency curve. The mode, mean, standard deviation and probable error of the mean are determined.

RESULTS

Measurements for untreated animals form curves with modes falling at 3.75 microns (chart 1). The mean heights of the cells calculated

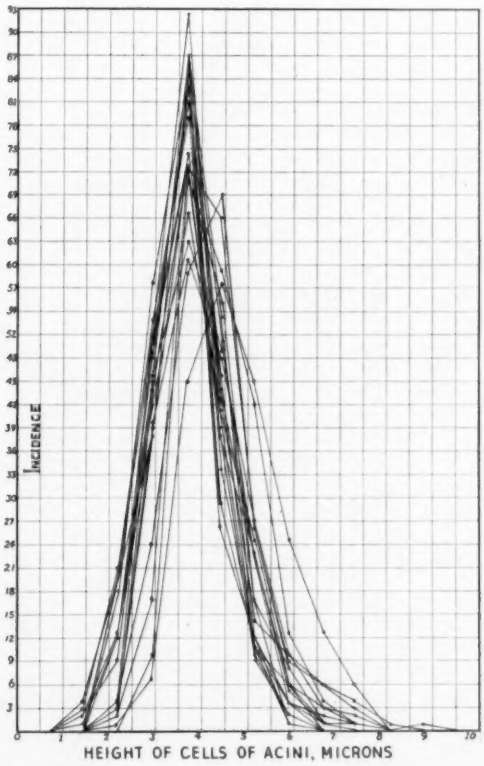

Chart 1.—Composite curves for 18 normal untreated guinea pigs. The mean cell heights in the glands ranged from 3.5 to 4.86 microns. The average mean for all the animals was 3.94 microns.

from the curves for 18 control animals measured in July, November, December and February ranged from 3.69 to 3.95 microns. This indicates a rather extraordinary uniformity of control material that is worthy of further investigation. It may be actual, as a result of uniform

diet and breeding, or the variations in hyperplasia apparent to other observers in control animals may not affect enough of the mature acini to shift the curve. Since the condition of this control material is fundamental for the method as it is now arranged, a more detailed analysis of control animals is in progress.

Serial sections cut from the thyroid gland of a control animal and that of an animal treated with thyrotropic substance were measured by the same observer (chart 2). The modes of the five curves from the five successive serial sections of the gland of the control animal were all at 3.75 microns. The mean heights of the cells ranged from 3.6 to 3.98 microns. The modes of five curves from similar sections of the gland of the treated animals were double, at 4.5 and 6 microns. The mean heights of the cells ranged from 6.06 to 6.24 microns. Thus, there was a similar degree of variation in the serial sections and in the control series. The difference in the control glands was 3.95 — 3.69, or 0.26 microns; the differences in the serial sections were 3.98 — 3.60, or 0.38 microns, and 6.24 — 6.06, or 0.18 microns.

Data on Treatment with a Preparation of the Anterior Lobe of the Hypophysis

Experiment No.	Dose, Cc.	No. of Glands Counted	Modes, Microns	Range of Means, Microns	Average of Means, Microns
1	Controls	18	3.75	3.59-4.1	3.77 ± 0.015
2	0.0025	12	4.5	4.5-4.8	4.65 ± 0.018
3	0.0050	8	4.5-6	4.9-5.6	5.25 ± 0.02
4	0.0100	5	4.5-6	5.5-6	5.71 ± 0.029
5	0.0200	5	5.25-6.75	6.1-6.4	6.14 ± 0.028

A preparation of the anterior lobe of the bovine hypophysis [14] containing thyrotropic principle was administered subcutaneously for three days. After treatment with three daily doses of 0.0025 cc. each, the curves had a mode at 4.5 microns (chart 3 *A*). The mean heights of the cells of 8 such animals ranged from 4.5 to 4.8 microns. After treatment with three daily doses of 0.005 cc. each, the mode for 8 animals was 4.5 microns (chart 3 *B*), but the mean heights ranged from 4.9 to 5.6 microns. After 0.01 cc. doses the curves were bimodal, at 4.5 and 6 microns (chart 4 *A*); the mean heights for 5 animals ranged from 5.5 to 6 microns. After 0.02 cc. the curves also were bimodal, at 5.25 and 6.75 microns (chart 4 *B*), and the mean heights for 5 animals ranged from 6.1 to 6.4 microns. These data are shown in the accompanying table.

Still greater shifts of the curve to the right was evident with 0.05 and 0.1 cc. doses. The general rule seems to be established that there is an increasing shift to the right with increasing doses. This is illustrated in a composite curve (chart 5).

14. The preparation used was antuitrin —T, supplied by Parke, Davis & Co.

CLINICAL STUDIES

The present clinical report on the urinary assay of thyrotropic substance is presented merely as an indication of the direction the study is taking. Extracts from larger quantities of urine, it is thought, will bring out the same clinical relations more clearly.

Fifty cubic centimeters of urine collected early in the morning was chilled and filtered, mixed with 450 cc. of acetone and allowed to stand for twenty-four hours. The supernatant fluid was siphoned off, and the residue was centrifuged. The precipitate was washed twice with absolute alcohol and twice with anhydrous ether. Ten cubic centimeters of water was then stirred with the precipitate, and

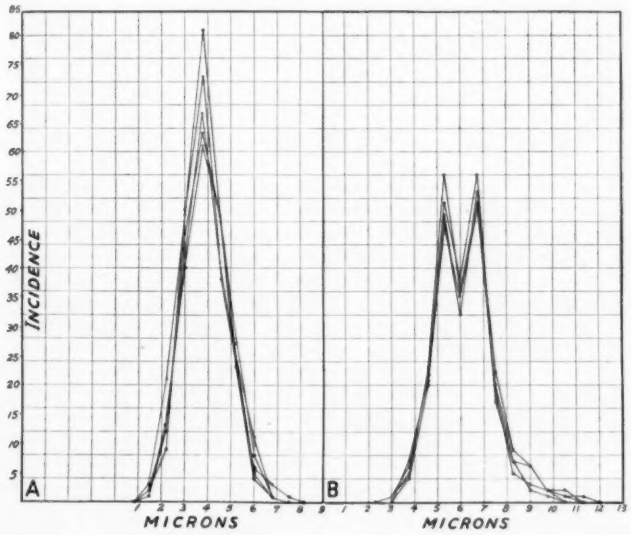

Chart 2.—*A*, frequency curves for five successive serial sections from the thyroid gland of an untreated guinea pig. The mode was 3.75 microns and the mean 3.79 microns. *B*, frequency curves for five successive serial sections from the thyroid gland of a guinea pig treated with three daily injections (0.02 cc. each) of a preparation of the anterior lobe of the hypophysis. The curves were bimodal, at 4.5 and 6 microns. The mean was 6.15 microns.

this was allowed to stand for two or three hours and then centrifuged. The supernatant aqueous solution was given by subcutaneous injection in divided doses during three days to an immature female guinea pig weighing approximately 200 Gm. Whenever possible duplicate studies were made.

Such material from 21 young men and women, apparently normal, whose basal metabolic rates ranged from —9 to + 11 per cent (Aub-

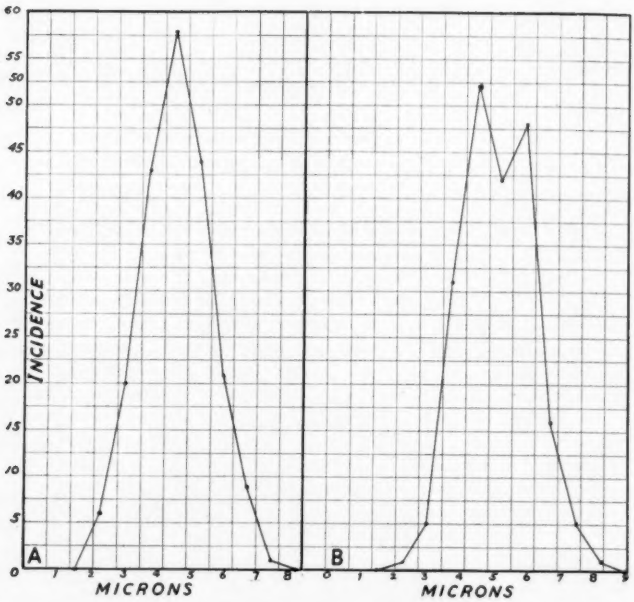

Chart 3.—*A*, curve for the thyroid gland of a guinea pig which received three daily doses of 0.0025 cc. each of a preparation of the anterior lobe of the hypophysis. The mode was 4.5 microns and the mean cell height 4.57 microns. *B*, curve for the thyroid gland of a guinea pig which received three daily doses of 0.005 cc. each of a preparation of the anterior lobe of the hypophysis. The mean cell height was 5.12 microns.

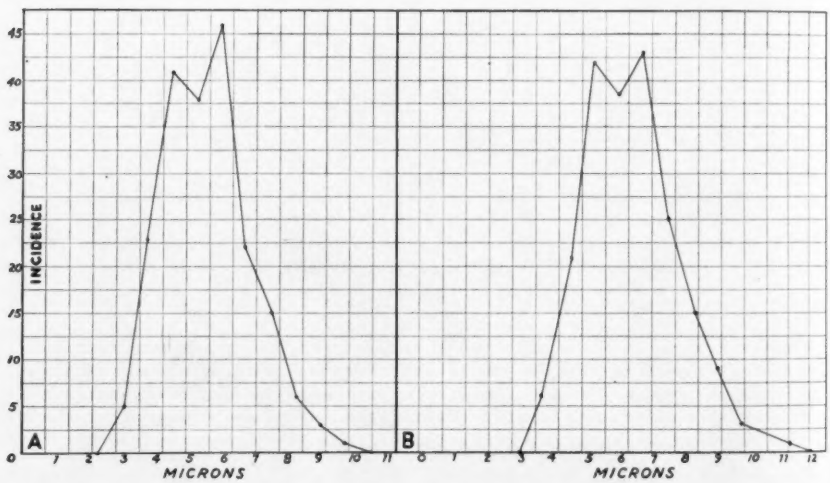

Chart 4.—*A*, curve for the thyroid gland of guinea pig which received three daily doses of 0.01 cc. each of a preparation of the anterior lobe of the hypophysis. The mean cell height was 5.54 microns. *B*, curve for the thyroid gland of a guinea pig which received three daily doses of 0.02 cc. each of a preparation of the anterior lobe of the hypophysis. The mean cell height was 6.36 microns.

Du Bois) produced a slight but definite shift to the right of the control curve (chart 6). The mean heights of the cells ranged from 3.49 ± 0.038 to 5.04 ± 0.042 microns with an average of 4.12 microns.

The difference between the average mean height of the cells of the thyroid glands of the control guinea pigs and that of the guinea

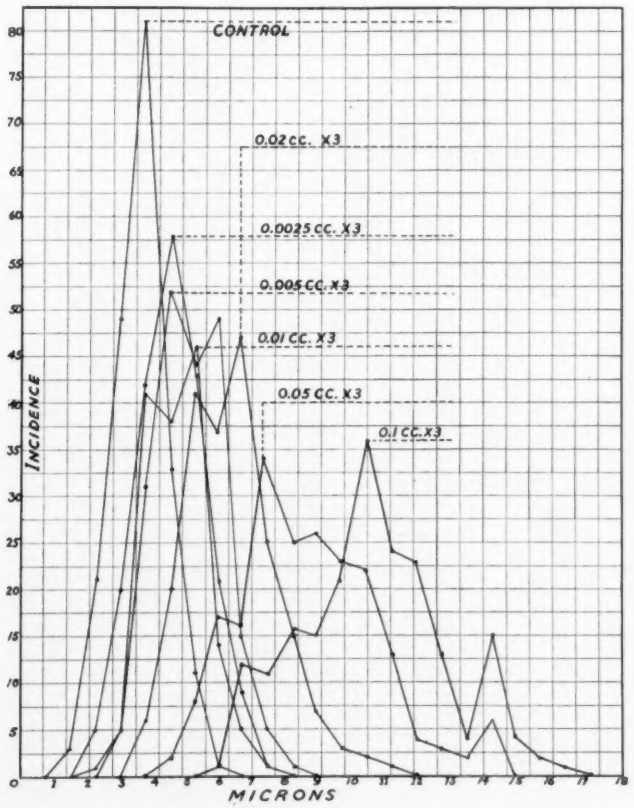

Chart 5.—A composite picture of the curves obtained with increasing doses. Note the shift to the right produced by increasing the dosage.

pigs treated with extract of urine from normal persons, e. g., 4.39 ± 0.029 to 3.77 ± 0.015 microns, was great enough to be of statistical significance as compared with the probable error in the measurements of the cells of the control glands (0.015 microns).

Such material from a group of older men and women who were not myxedematous but whose basal metabolic rates ranged from —34 to —17 per cent and who showed values for blood cholesterol ranging from 220 to 305 mg. per hundred cubic centimeters produced a further shift to the right in the curve (chart 7). The mean heights of the cells ranged from 3.93 ± 0.028 to 5.92 ± 0.04 microns with an average mean of 4.7 microns.

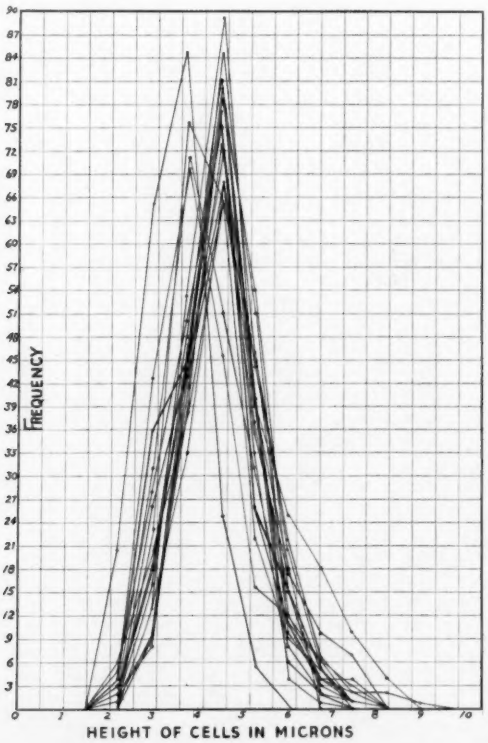

Chart 6.—A composite graph of the twenty-one curves for guinea pigs which were given injections of extract of urine from 21 normal persons whose basal metabolic rates ranged from —9 to + 11 per cent. The mean cell heights ranged from 3.84 to 5.04 microns. The average was 4.4 microns.

Such material from 3 men who had had total thyroidectomy for heart disease, who had not received thyroid therapy but who were not completely myxedematous and whose basal metabolic rates ranged from —31 to —2 per cent produced still greater shift to the right

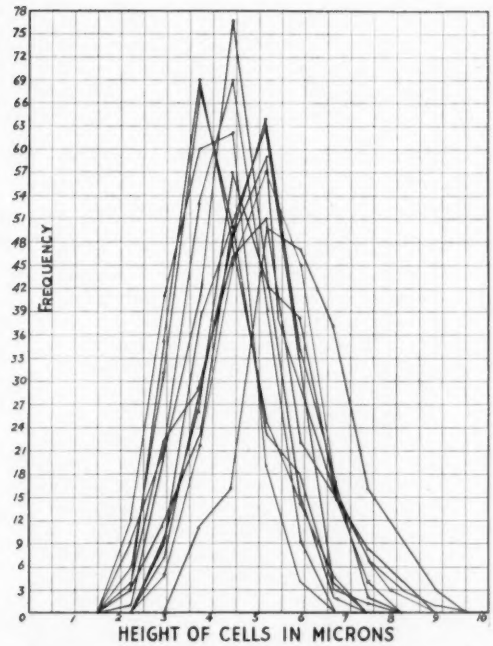

Chart 7.—A composite graph of the sixteen curves for guinea pigs which were given injections of extract of urine from 8 patients with low basal metabolic rates, ranging from —16 to —34 per cent, but without clinical signs of myxedema. The mean cell heights ranged from 3.93 microns (controls) to 5.92 microns.

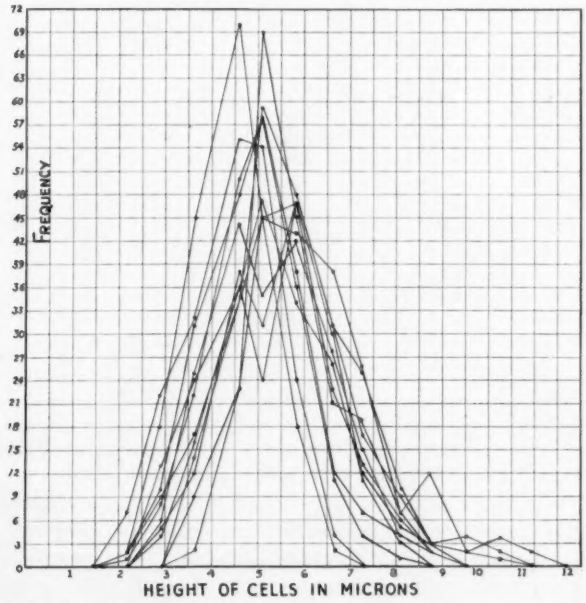

Chart 8.—A composite graph of the twelve curves for guinea pigs which were given injections of extract of urine from 3 patients after total thyroidectomy. The mean cell heights ranged from 4.5 to 6.34 microns, with an average of 5.49 microns.

(chart 8). The mean heights of the cells ranged from 4.5 ± 0.029 to 6.34 ± 0.05 microns with an average mean of 5.4 microns.

Such material from 14 patients with hyperthyroidism, whose basal metabolic rates ranged from + 8 to + 90 per cent, produced no shift

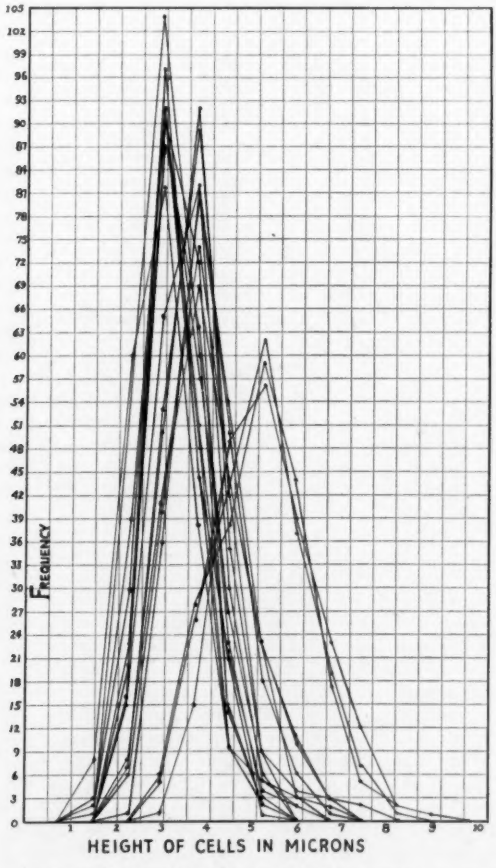

Chart 9.—A composite graph of the twenty-nine curves for guinea pigs which received injections of extract of the urine of 14 patients with hyperthyroidism, the basal metabolic rates ranging from + 8 to + 90 per cent. The mean cell heights ranged from 2.96 to 5.44 microns, with an average of 3.53 microns.

in the curve to the right with 2 exceptions (chart 9). Four of these patients who showed negative results of assays for thyrotropic substance in the urine had exophthalmos. The mean heights of the cells

ranged from 2.96 ± 0.02 to 5.44 ± 0.03 microns, with an average mean of 3.53 microns.

The possibility that an excess of iodine in the urine of patients with hyperthyroidism would obliterate the effect of any thyrotropic substance present is not completely contradicted, but the addition of 50

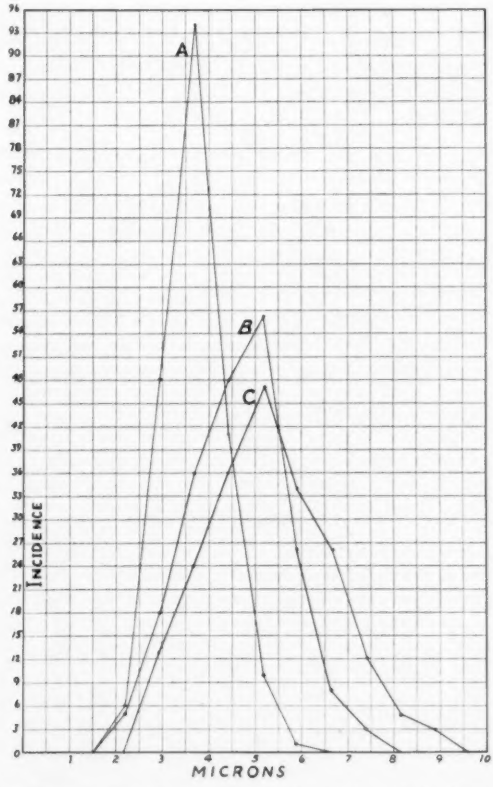

Chart 10.—Curves for guinea pigs which received injections of extract of urine from a patient after total thyroidectomy. *A*, the urine was heated in order to destroy the thyrotropic substance. *B*, 50 micrograms of iodine was added (physiologic in hyperthyroidism). *C*, the usual treatment of the urine was employed.

micrograms of iodine to the 50 cc. sample of urine from a patient with hypothyroidism following total thyroidectomy did not obliterate that effect (chart 10). This amount of iodine is the aliquot calculated from

the excess of physiologic iodine known to be excreted in hyperthyroidism.[15] Heating a specimen from this patient did prevent the effect, since thyrotropic substance is destroyed by heat (chart 10).

SUMMARY AND CONCLUSIONS

The increased height of the acinar epithelium of the guinea pig thyroid induced by thyrotropic substance may be found by direct micrometer measurements, and the hyperplasia throughout the gland may be represented by a frequency curve derived from these measurements.

Increasing doses of a solution containing thyrotropic substance produce increasing shifts of such curves to the right.

The extract of 50 cc. of urine of normal persons produces a slight shift to the right.

An extract of 50 cc. of urine of nonmyxedematous persons with a low basal metabolic rate may or may not produce a greater effect.

The extract of 50 cc. of urine of men totally thyroidectomized for heart disease produced a still greater effect.

The extract of 50 cc. of urine of men and women with hyperthyroidism, with or without exophthalmos, produced no effect except in 2 cases (the occurrence of these exceptions cannot be explained).

15. Curtis, G. M.: Iodine Relationships of Thyroid Disease, Surg., Gynec. & Obst. **62**:365-371, 1936.

THE EXTERNAL SECRETORY FUNCTION OF THE HUMAN PANCREAS

PHYSIOLOGIC OBSERVATIONS

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ST. LOUIS

The earliest basic knowledge of the physiology of the external function of the pancreas came largely as a result of the pioneer studies of two eminent experimental physiologists, Claude Bernard [1] and Ivan Pavlov.[2] The former, in 1856, showed that pancreatic juice is highly essential to digestion; the latter, in 1902, demonstrated the existence of pancreatic enzymes. In the same year Bayliss and Starling [3] investigated the factors concerned in the secretory stimulus of the pancreas and assigned the important role to a humoral mechanism which they named secretin.

Many valuable contributions to the physiology of the pancreas have been made during the past thirty years, and McClure [4] in a recent paper has enumerated as follows the important physiologic facts which are now firmly established: 1. Stimulation of the external secretion of the pancreas is of humoral origin, but the exact mechanism remains undetermined. 2. The ingestion of food is followed by secretion of pancreatic juice. 3. The external secretion of the pancreas plays an essential role in digestion. To these facts should perhaps be added the

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Based on material presented in lantern slides by Dr. J. M. McCaughan, at the Eighty-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 10, 1937.

1. Bernard, C.: Mémoire sur le pancréas et sur le rôle du suc pancréatique dans les phénomènes digestifs, particulièrement dans la digestion des matières grasses neutres, Paris, J. B. Ballière, 1856.

2. Pavlov, Ivan: The Work of the Digestive Glands, translated by W. H. Thompson, London, C. G. Griffin & Co., 1902.

3. Bayliss, W. M., and Starling, E. H.: The Mechanism of Pancreatic Secretion, J. Physiol. **28**:325-353, 1902.

4. McClure, Charles W.: Observations on the Physiology and Pathologic Physiology of External Pancreatic Functions, Rev. Gastroenterol. **3**:1-26, 1936.

observations of Elman and McCaughan [5] on the rapidly fatal effect in experimental animals of the complete loss of pancreatic juice by total drainage through a fistula.

The greater part of the information regarding the external function of the pancreas has been derived either from experiments conducted on lower animals or by indirect experiments on human beings in which the pancreatic juice mixed with other intestinal secretions is obtained for study ordinarily by means of the Rehfuss tube. Considerable interest attaches therefore to reports of clinical experiments performed directly on man. Such observations are possible in cases of pancreatic fistula, and physiologic data of immense value have been accumulated in this manner. The literature contains a great number of case reports dealing with pancreatic fistula, but emphasis is largely given to discussions of the varied pathogenesis and of technical methods of securing closure. Fortunately in a small number of the cases, however, careful chemical and physiologic investigations have been made, with the result that knowledge of human pancreatic physiology has been enriched.

REPORT OF A CASE

The patient, a man aged 49, was admitted to the Firmin Desloge Hospital on Jan. 15, 1936, for surgical closure of a pancreatic fistula which had followed a Billroth II type of gastric resection performed elsewhere. The patient stated that the fistula had been draining for more than nine months. The Wohlgemuth antidiabetic treatment had been instituted during this time in an endeavor to bring about healing of the fistula, but the result was unsatisfactory.

On physical examination the patient appeared markedly undernourished. There were a few coarse rales in the left upper portion of the chest posteriorly, but otherwise the thorax was normal. There was an old median operative scar in the upper part of the abdomen, and about 4 cm. below the xiphoid process was a tiny cutaneous opening which barely admitted the tip of a small probe. The surrounding skin appeared normal. A clear watery fluid was flowing profusely from this opening, and a sample was collected for identification and study. The systolic blood pressure was 125 mm. of mercury and the diastolic pressure 94 mm. On laboratory examination the urine was normal except for an occasional leukocyte and erythrocyte. The blood count showed 7,900 leukocytes and 3,940,000 erythrocytes. The hemoglobin value was 13 Gm. A differential count was normal. The clotting time and bleeding time were both normal, as was the clot retraction time. The sugar, nonprotein-nitrogen, carbon dioxide and chloride values for the blood were within normal limits. A sugar tolerance test by the Shaffer-Hartmann method gave a curve within the normal zone. The Wassermann and Kahn tests of the blood gave negative reactions. Examination of the sputum revealed no abnormality. Gastric analysis showed normal free and combined acids. Roentgenograms of the chest were essentially normal. Fluoroscopic examination of the upper portion of the gastro-intestinal tract showed that the esophagus was normal, the stomach had been resected at its distal third and a gastro-enterostomy

5. Elman, Robert, and McCaughan, John M.: On the Collection of the Entire External Secretion of the Pancreas Under Sterile Conditions and the Fatal Effect of Total Loss of Pancreatic Juice, J. Exper. Med. **45**:561-570, 1927.

stoma had been made 2 inches (5 cm.) proximal to the blind end. The barium sulfate passed freely through the stoma.

On February 1 the fistula was implanted into the anterior wall of the stomach by a method reported elsewhere. The patient made a satisfactory recovery and was discharged from the hospital on March 15. Twelve months after the operation he reported that he had remained entirely well.

Experimental Procedure.—Physiologic studies were made previous to operation, and the response to various excitatory and inhibitory drugs and foodstuffs was recorded. A small glass funnel was first applied to the skin about the opening of the fistula and was held there with adhesive tape. The patient was placed in the prone position on two tables set end to end in such a manner that the secretion could drop between the tables and into the recording and collecting apparatus. At least two hours was permitted to elapse after a meal before the beginning of the experiment. Samples of the secretion were collected at regular intervals, usually every fifteen minutes. The total alkali in each specimen was titrated with tenth-normal hydrochloric acid, and the rate of flow was measured before and after each experiment.

Experimental Results.—In order not to submit the patient to the risk of possible infection through introduction of a cannula into the fistula, the total volume of pancreatic juice discharged in twenty-four hours was estimated by calculations based on the average rate of flow noted during numerous experiments. An approximate estimate of 600 cc. per diem was obtained. The amount of secretion was found to be least during fasting and greatest after meals.

Comment.—In the twenty-seven investigations reviewed by us regarding the amount of pancreatic juice discharged from a pancreatic fistula, the least amount (30 to 40 cc.) was recorded by Graf [6] and the largest (1,186 cc.) by Snyder and Lium.[7]

Ellinger and Cohn [8] were among the first (1905) to note that the secretion of pancreatic juice in human beings is continuous. Since then this observation has been confirmed many times.[9]

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6. Graf, P.: Zur Kasuistik der traumatischen Pankreaszysten, München. med. Wchnschr. **57**:2529-2531, 1910.

7. Snyder, William H., and Lium, Rolf: Pancreatic Fistula, Surg., Gynec. & Obst. **62**:57-64, 1936.

8. Ellinger, A., and Cohn, M.: Beiträge zur Kenntnis der Pankreassekretion beim Menschen, Ztschr. f. physiol. Chem. **45**:28-37, 1905.

9. (*a*) Babkin, B. P.: Die aeussere Sekretion der Vardauungsdruesen, ed. 2, Berlin, Julius Springer, 1928, pp. 452-629. (*b*) von Friedrich, Ladislaus: Ein Fall von Pankreasfistel, Klin. Wchnschr. **1**:1658, 1922. (*c*) Glaessner, K., and Popper, H.: Zur Physiologie und Pathologie des Pankreasfistel-Sekretes, Deutsches Arch. f. klin. Med. **94**:46-60, 1908. (*d*) Holsti, O.: Beiträge zur Kenntnis der Pankreassekretion beim Menschen, ibid. **111**:48-92, 1913. (*e*) Kahn, J., and Klein, H. M.: Human Pancreatic Secretion Studies from a Case of Pancreatic Cyst with Fistula, Am. J. M. Sc. **184**:503-511, 1932. (*f*) Kogut, B.; Matzner, J., and Sobel, A. E.: A Study of External Pancreatic Secretion in Man, J. Clin. Investigation **15**:393-396, 1936. (*g*) Rivier, P.: Contribution à l'étude de la fonction pancréatique chez l'homme; cas de rupture traumatique du pancréas, Compt. rend. Soc. de biol. **97**:699-670, 1927. (*h*) Weaver, M. M.; Luckhardt, A. B., and Koch, F. C.: Preparation of a Potent Vaso Dilatin-Free Pancreatic Secretin, J. A. M. A. **87**:640-645 (Aug. 28) 1926.

CHEMICAL COMPOSITION OF HUMAN PANCREATIC JUICE

The chemical composition of human pancreatic juice has been so adequately studied by others, notably Ellinger and Cohn,[8] Friedrich,[9b] Glaessner,[10] Glaessner and Popper,[9c] Holsti,[9d] Kahn and Klein,[9e] Schumm [11] and Villard and Labry,[12] that we felt little would be accomplished by repetition of their work. Our investigation, therefore, was limited to relatively few determinations, and these were carried out mainly for the purpose of identification. The fluid was watery; at times it was clear and at other times opalescent. Sometimes a slightly yellow tinge was noticeable. The specific gravity of a single specimen was 1.005, and the p_H was 8.65. The reaction was alkaline to methyl red, and the titrable alkalinity was equivalent to 65 cc. of tenth-normal alkali to 100 cc. of the fluid. A trace of protein was shown to tests with acetic acid and ferrocyanide. Lipase, amylase and inactive trypsin were present.

EFFECT OF HORMONES, DRUGS AND FOODSTUFFS ON THE RATE OF SECRETION AND ON THE TOTAL BASE

The curves of secretion showed considerable fluctuation, and our conclusions have been based on the difference between the average rate before and the average rate after the administration of the substance under investigation. In some curves the initial rate appeared greatest. The explanation is that the fistula tract acted as a reservoir while the subject was in the recumbent position, and several cubic centimeters of pancreatic juice necessarily accumulated. When the patient was turned face down, the tract emptied rapidly and gave an apparent but false picture of active secretion. We therefore waited until the rate became fairly constant before beginning the experiments.

1. *Secretin.*—A protein-free secretin was prepared according to the method of Weaver, Luckhardt and Koch [9h] and was sterilized before being used. This preparation was tested for possible toxic action on both dogs and guinea pigs. The effect of the secretin preparation on an unanesthetized dog with a pancreatic fistula is shown in chart 1.

The first experiment (chart 1), in which 2 cc. of secretin was injected intramuscularly in our subject, showed a marked rise in total base which lasted for between fifteen and thirty minutes and an increase in the rate

10. Glaessner, K.: Ueber menschliches Pankreassekret, Ztschr. f. physiol. Chem. **40**:465-479, 1903-1904.

11. Schumm, O.: Ueber menschliches Pancreassecret, Ztschr. f. physiol. Chem. **36**:292-332, 1902.

12. Villard, M., and Labry, R.: Pseudo-kyste du pancréas: Fistule pancréatique post-operatoire; remarques physiologiques et thérapeutiques, Lyon méd. **142**:424-428, 1928.

of flow from an average of 3 drops a minute to an average of 7 drops a minute. After a second injection of 3 cc. of secretin fifteen minutes later there was no further response. A second experiment with secretin (chart 7) in which the total base was not determined showed a rise in the rate of secretion from an average of 6.4 drops to an average of 10 drops a minute after injection of 2.5 cc. of secretin intramuscularly, but no further rise occurred after two subsequent injections of 2.5 cc.

Comment: The effect of our preparation of secretin on the dog was similar to that observed by other investigators.[13] Secretin when administered to the human subject produced a definite increase in the rate of secretion. Snyder and Lium reported inconclusive results after an injection of 6 mg. of secretin. The flow of pancreatic juice has been much more pronounced and constant after the administration of secretin in animals than it has been in human beings. McClure has suggested that

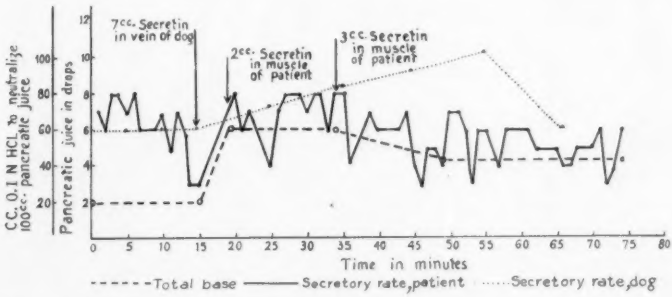
7cc. Secretin in vein of dog
2cc. Secretin in muscle of patient
3cc. Secretin in muscle of patient
CC. 0.1 N HCl to neutralize 100cc. pancreatic juice
Pancreatic juice in drops
Time in minutes
Total base
Secretory rate, patient
Secretory rate, dog

Chart 1.—The effect of secretin on the external secretory function of the human pancreas (secretory curve of a control animal is also shown).

this result can be explained by the marked habitual differences in the diets of dogs and of human beings, that of the latter being more complex.

2. *Water.*—This experiment was begun four hours after the last meal. The flow was observed for thirty minutes and was found to average 3 drops a minute. At the end of this period the patient drank 150 cc. of water (chart 7). An increase in flow began almost immediately and averaged about 7 drops a minute for ten minutes.

Comment: Snyder and Lium similarly obtained an immediate and striking response after the administration of water by mouth. Ivy [13c] has shown that when a given quantity of water is taken by mouth and

13. (*a*) Farrell, J. I., and Ivy, A. C.: Contributions to the Physiology of the Pancreas: II. The Proof of a Humoral Mechanism of External Pancreatic Secretion, Am. J. Physiol. **78**:325-338, 1926. (*b*) Graf.[6] (*c*) Ivy, A. C.: Studies in Water Drinking, Am. J. Physiol. **46**:420-442, 1918. (*d*) McClure.[4]

then immediately aspirated from the stomach by tube and measured, a small portion (5 to 10 cc.) of the water is lost almost instantly into the duodenum along with the gastric secretogogues. This may be the cause of the increased flow after the drinking of water.

3. *Beef Broth.*—Fifty cubic centimeters of beef broth was given by duodenal tube. A slight rise in rate of secretion and a fall in total base from 100 to 68 took place (chart 7).

Comment: The results of animal experiments with pure foodstuffs with regard to the amount of pancreatic juice secreted and the concentration of enzymes are not always applicable directly to man. Most observers, however, hold that the flow is greatest after the taking of carbohydrate, less after the taking of protein and least after the taking

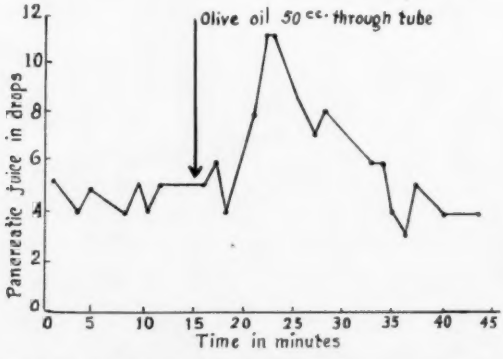

Chart 2.—The effect of olive oil on the external secretory function of the human pancreas.

of fat. In secretion curves after the administration of protein Holsti noted an initial rise, followed by a fall to zero until the middle of the second hour, and then a second rise which reached a maximum in either the third or the fourth hour.

4. *Olive Oil.*—Fifty cubic centimeters of olive oil was given by tube. The rate began to increase almost immediately, reaching 11 drops a minute in seven minutes and gradually falling to 4 drops a minute twenty-five minutes later. The total base was not determined in this experiment (chart 2).

Comment: Ivy [13e] applied olive oil to the jejunal fistula of a dog and observed no increase in rate of secretion in a transplant of the pancreas in which the normal blood and nerve supply had been completely excluded. Most observers record the largest volume of pancreatic secre-

tion after a carbohydrate meal and the least amount after fatty foods, but Mocquot, Joltrain and Laudat [14] obtained the least response after a meal of meat.

5. *Dextrose.*—Fifty cubic centimeters of 50 per cent dextrose was introduced into the tube. An immediate rise from about 7 drops a minute to 13 drops a minute was noted, but after about ten minutes the rate fell from a mean level of 10 drops a minute to 5.5 drops a minute, and this level was maintained for twenty minutes, after which the experiment was terminated. The total base fell from 65 to 44 after the introduction of dextrose (chart 3).

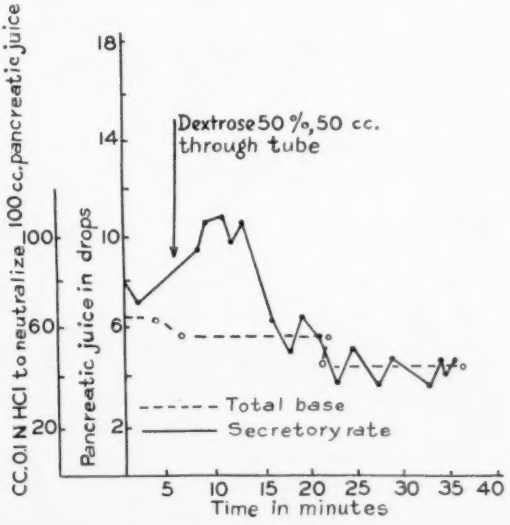

Chart 3.—The effect of dextrose on the external secretory function of the human pancreas.

Comment: Snyder and Lium observed a slow response to dextrose and attributed it to a delayed emptying time of the stomach caused by the hypertonic solution. This explanation may not hold in our case because of the fact that the pyloric sphincter had been resected along with the antrum of the stomach. Holsti [9d] and Wohlgemuth [15] obtained a rise after the administration of pure carbohydrate.

14. Mocquot; Joltrain, E., and Laudat: Abcès du pancréas d'origine colibacillaire; fistule avec écoulement de suc pancréatique; étude des sécrétions externes et internes du pancréas, Rev. de méd., Paris **50**:231-245, 1933.

15. Wohlgemuth, J.: Zur Therapie der Pankreasfistel nebst Bemerkungen über den Mechanismus der Pankreassekretion während der Verdauung, Berl. klin. Wchnschr. **45**:389-393, 1908.

6. *The Mixed Meal.*—A meal containing the average amounts of fat, carbohydrate and protein of the ordinary general hospital diet was given. The meal was finished in fifteen minutes, and observations were carried on for an additional twenty minutes. A slight rise in rate of flow and a slight fall in total base were noted (chart 7).

Comment: According to Pavlov, when pure foodstuffs are given and the volume of pancreatic juice secreted is observed in experimental animals, it is found that the greatest amount follows the giving of carbohydrate, a less amount follows that of protein and the least amount of all that of a fat meal. In human beings the findings have been more variable, but in general they have tended to parallel, in the main, the

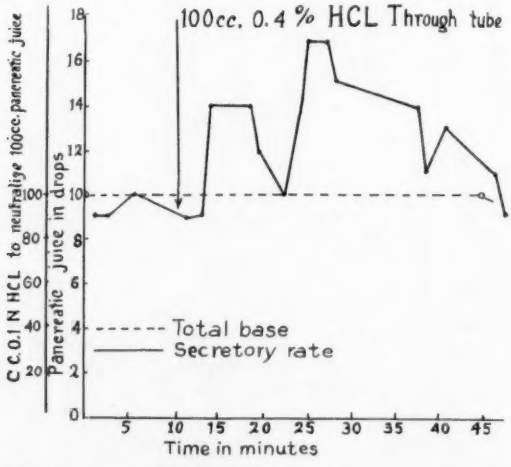
100cc. 0.4 % HCL Through tube
c.c. 0.1 N HCL to neutralize 100cc. pancreatic juice
Pancreatic juice in drops
Total base
Secretory rate
Time in minutes

Chart 4.—The effect of hydrochloric acid on the external secretory function of the human pancreas.

results in animal experiments. In the majority of the studies of human beings the diets used have been mixed, with one or another of the primary foodstuffs predominating. Wohlgemuth [15] stated as his conclusion that the secretory curve after a mixed meal is a composite of the individual food constituents making up the meal.

7. *Hydrochloric Acid.*—One hundred cubic centimeters of 0.5 per cent solution of hydrochloric acid was given through a Rehfuss tube introduced directly into the jejunum. A sharp rise in rate of secretion from 9 to 13 drops a minute was noted. There was no change in total base (chart 4).

Comment: Bayliss and Starling have shown that the introduction of acid into the duodenum of animals causes a rise in rate of flow, and

they said that this phenomenon could be accounted for by the stimulation to secretin formation thus caused. Sawitsch [16] and Ciminata [17] found that the flow induced by hydrochloric acid is richer in alkali but poorer in ferments and that the so-called "nervous" type of secretion is poorer in alkali but richer in ferments. Our results differed from these results of experiments performed on animals, in that the total base was not affected.

8. *Peptone.*—One hundred cubic centimeters of 10 per cent solution of peptone was given through the tube. The secretory rate rose rapidly from 5 to a maximum of 11 drops a minute and later fell again to 5 drops a minute. There was no change in the total base (chart 7).

Comment: Popielski,[18] working with dogs, reported a diminished effect of gastric juice in evoking pancreatic secretion by inactivating hydrochloric acid with peptone. Hydrochloric, sulfuric, phosphoric, oxalic, acetic, tartaric and citric acid all had their effects weakened ten to twelve times by the addition of peptone. In all cases the activity of the acids in evoking pancreatic secretion was proportional to the hydrogen ion concentration.

9. *Sodium Bicarbonate.*—Sodium bicarbonate produced no significant change in rate (a fall from an average of 5 to 4.5 drops per minute), but a definite elevation in total base occurred, followed later by a fall below the previous level (chart 5).

Comment: Some observers have noted an inhibitory effect after exhibiting sodium bicarbonate, but Karewski,[19] Pavlov [2] and Glaessner and Popper [9c] have denied that it has any effect on pancreatic secretion. The use of sodium bicarbonate in conjunction with a diet low in carbohydrate is an integral part of the method advocated by Wohlgemuth as an ajd to encouraging closure of a pancreatic fistula.

10. *Coffee.*—Coffee caused a delayed rise in rate and an increase in total base from 38 to 84 (chart 7).

11. *Bile Salts.*—Bile salts caused a fall in rate and in total base (chart 7).

Comment: Ivy and Lueth [20] and Mellanby [21] reported an increase in the flow of pancreatic juice after the exhibition of bile.

16. Sawîtsch, W. W.: Beiträge zur Physiologie der Pankreassaftsekretion, Zentralbl. f. d. ges. Physiol. u. Path. d. Stoffwechs. **4**:1-18, 1909.

17. Ciminata, A.: La secrezione esterna del pancreas dopo esclusione pilorica e gastro-digiunostomia a Y di Roux, Arch. di fisiol. **23**:304-317, 1925.

18. Popielski, L.: Die Wasserstoffionen und die sekretorische Tätigkeit der Bauchspeicheldrüse, Arch. f. d. ges. Physiol. **174**:152-176, 1919.

19. Karewski, F.: Zur Diagnose und Therapie der Pankreascysten, Deutsche med. Wchnschr. **16**:1035-1037, 1890.

20. Ivy, A. C., and Lueth, H. C.: On Bile Stimulation of Pancreatic Secretion, Proc. Soc. Exper. Biol. & Med. **24**:837, 1927.

21. Mellanby, John: Mechanism of Pancreatic Secretion, Lancet **2**:215-218, 1926.

12. *Magnesium Sulfate.*—Thirty cubic centimeters of a 15 per cent solution of magnesium sulfate caused no appreciable change in either rate or total base (chart 7).

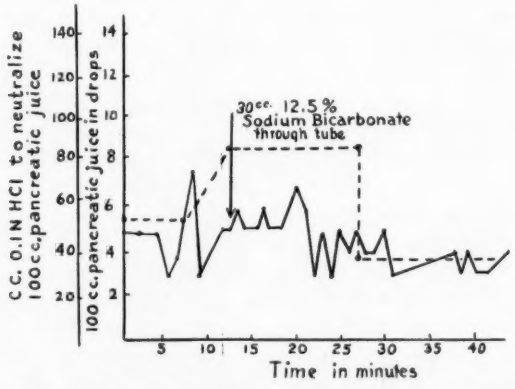
C.C. 0.1 N HCl to neutralize 100 c.c. pancreatic juice
100 c.c. pancreatic juice in drops
30 cc. 12.5% Sodium Bicarbonate through tube
Time in minutes

Chart 5.—The effect of sodium bicarbonate on the external secretory function of the human pancreas.

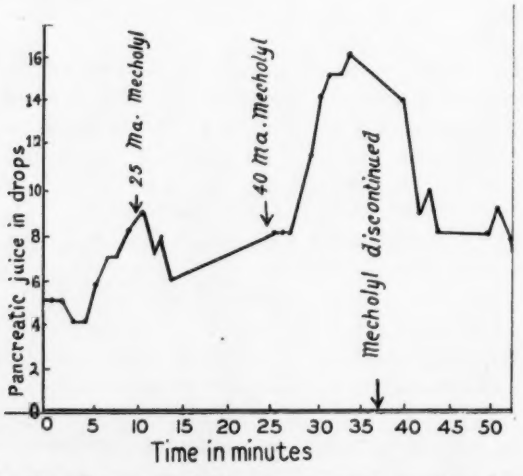

Chart 6—The effect of mecholyl on the external secretory function of the human pancreas.

13. *Mecholyl.*—One-tenth per cent mecholyl was given by iontophoresis, the electrodes being placed on the front and back of the thorax. With 25 milliamperes of current, the rate of secretion rose from 5 to 8 drops a minute. After fifteen minutes the current was raised to 40

milliamperes, and the rate increased sharply to a maximum of 16 drops a minute. The current was discontinued twenty-seven minutes after the experiment was begun, and the rate returned to normal fifteen minutes later (chart 6).

Comment: Mecholyl exerts an excitatory effect on the parasympathetic innervation. This drug proved to be the most powerful stimulus to the flow of pancreatic juice of any used in our experiments. The effect noted is due, we believe, to stimulation of the parasympathetic nerve fibers supplying the pancreas.

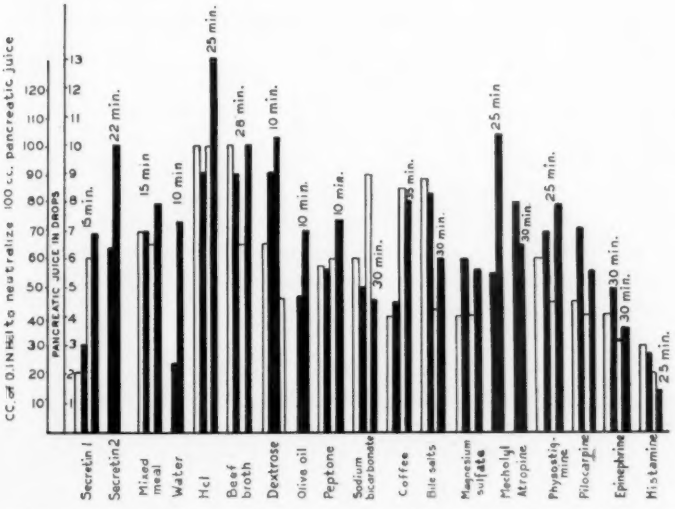

Chart 7.—Summarizing the effect of the administration of various substances on the total base and on the rate of secretion of human pancreatic juice. The white columns indicate the total base before and after the onset of the experiment. The black columns indicate the secretory rates before and after the onset of the experiment. The time of maximum duration is indicated above the columns.

14. *Atropine.*—Atropine, 1/100 grain (0.006 Gm.), was given intramuscularly. A slight fall in rate occurred after ten minutes. The total base was not measured (chart 7).

Comment: Atropine has been found to diminish the secretion.[22] Snyder and Lium, besides reporting a diminution caused by atropine, stated that the expected hourly rise after meals was converted into a fall which lasted about an hour.

22. Villaret, M., and Justin-Besançon, L.: Physiologie de la sécrétion pancréatique de l'homme étudiée par la fistulisation du canal de Wirsung, Nutrition **6**:209-222, 1936. Weaver, Luckhardt and Koch.[9h] Glaessner.[10] Holsti.[9d]

15. *Physostigmine.*—Physostigmine, 1/50 grain (0.0013 Gm.), was given intramuscularly. No effect was noted for thirteen minutes, when a gradual rise in secretory rate began. The total base fell from 60 to 40 (chart 7).

16. *Pilocarpine.*—After an injection of 1/8 grain (0.008 Gm.) of pilocarpine hydrochloride into the muscle, both rate and total base fell slightly (chart 7).

Comment: The rise following the administration of physostigmine was anticipated. The negative results with pilocarpine were contrary to the effects obtained by others.[23] Snyder and Lium obtained a striking increase in rate of flow with much smaller doses of pilocarpine and physostigmine.

17. *Epinephrine.*—When epinephrine hydrochloride (0.005 Gm.) was given intramuscularly, a fall in rate began in five minutes and reached an average of 2 drops a minute, which was maintained for twenty-five minutes; the total base fell from 40 to 28 (chart 7).

Comment: These results are in accord with those of Anrep,[24] who obtained a fall in rate of flow by stimulation of the splanchnic nerves.

18. *Histamine.*—After the intramuscular injection of 0.0005 Gm. of histamine phosphate there was no significant change in rate, and there was only a slight fall in the total base (chart 7).

SUMMARY

Physiologic observations on the external secretory function of the human pancreas were made on a patient in whom a pancreatic fistula developed after a Billroth II type of gastric resection. The fistula was later successfully transplanted to the anterior wall of the stomach. Preceding the operation the effect on the rate of secretion and on the total base was determined before and after the administration of various drugs and foodstuffs.

The volume of pancreatic juice secreted in twenty-four hours was estimated at 600 cc. A rise in secretory rate (chart 7) followed the exhibition of secretin, a mixed meal, water, hydrochloric acid, beef broth, dextrose, olive oil, peptone, coffee, mecholyl and physostigmine. A fall in the secretory rate occurred after the exhibition of sodium bicarbonate, bile salts, magnesium sulfate, atropine, epinephrine and histamine. The total base was elevated after the administration of secretin, sodium bicarbonate and coffee and was depressed after the administration of a mixed meal, beef broth, dextrose, bile salts, physostigmine, epinephrine

23. Sawitsch.[16] Snyder and Lium.[7] Villard and Labry.[12]

24. Anrep, G. V.: The Influence of the Vagus on Pancreatic Secretion, J. Physiol. **50**:421-433, 1915-1916.

and histamine. There was no significant change in total base after the exhibition of hydrochloric acid, peptone and magnesium sulfate.

The literature on pancreatic fistula as far as it deals with similar observations on the physiology of the human pancreas has been reviewed, and the results of the investigations of others have been compared with our own results.

Dr. W. T. Coughlin, Professor of Surgery, St. Louis University School of Medicine, assisted in an advisory capacity.

ABSTRACT OF DISCUSSION

DR. HOWARD M. CLUTE, Boston: Dr. McCaughan is to be complimented not only on the valuable physiologic studies that he has made of his two patients with pancreatic fistula but also on the excellent results obtained with surgical treatment.

From the point of view of the general surgeon it is interesting to consider the method by which, in the course of gastric and pancreatic surgical treatment, pancreatic fistula is caused. In my experience with patients with acute pancreatitis in which a drain has been inserted into necrotic pancreatic tissue, a permanent pancreatic fistula has not resulted, although transient drainage of pancreatic secretion may occur.

In a recent case in which subtotal pancreatectomy was performed no escape of pancreatic fluid from the wound postoperatively was observed, although at operation I removed more than half the pancreas. In cases of resection of the stomach I have not seen the occurrence of postoperative fistula, although I have often taken out superficial portions of the pancreas with the tumor.

It appears to me that pancreatic fistula tends to develop when surgical intervention obstructs the main pancreatic duct and that no permanent fistula formation follows injury of only the pancreatic parenchyma.

After drainage of the biliary tract in acute pancreatic necrosis, the emptying of pancreatic secretion through the major duct is resumed in those cases in which recovery is obtained, and since the major duct is intact, no fistula forms. In partial resection of the pancreas the major and minor ducts are tied off at their distal ends, but nothing interferes with drainage through their proximal portions; hence a fistula does not form.

In cases of gastric resection, however, a different situation may arise owing to injury at operation either of the accessory duct of Santorini or even of the major pancreatic duct. Surgeons should realize that the accessory pancreatic duct may enter the duodenum as much as 1 inch (2.5 cm.) above the level of the papilla of Vater. When the duodenal stump is closed, therefore, after gastric resection, especial pains should be taken that the accessory pancreatic duct is not cut. I have shaved off the surface of the pancreas during gastric resection and have left large raw areas of pancreas without having a fistula form. I believe that injury to the pancreatic ducts themselves is necessary to fistula formation.

It is interesting to inquire why pancreatitis does not follow the transplantation of a pancreatic fistula into the stomach. Commonly bouts of cholangeitis follow anastomosis of the gallbladder and the stomach, yet there is no pancreatitis in cases in which the pancreas drains directly into the stomach after a fistula is transplanted. It is of course true that the pancreatic secretion is continuous both by day and by night, but this in itself does not seem an adequate explanation of

the problem. Further information on this subject may well be applied to cases of biliary intestinal anastomosis in the prevention of postoperative infection of the biliary tract.

Dr. William T. Coughlin, St. Louis: As I listened to Dr. McCaughan I was reminded of Beaumont, who took advantage of opportunity when it presented itself. I wish to compliment Dr. McCaughan on the zeal, care, skill and efficiency with which he has carried out his experiments. The amount of work is appalling, especially from the standpoint of an older man. This is a young man's work.

Several years ago, when some one was asked to discuss surgery of the pancreas, he said, "Well, it's a good deal like discussing the hepatology of Ireland." There was not much surgery of the pancreas. Now, through the efforts of the younger investigators, who are being trained in chemistry and physiology, the problems are gradually being solved. There is a considerable amount of surgical treatment of the pancreas today.

Treatment of the fistula has given surgeons trouble for a long time. Transplantation of the fistulous tract has been done for fistula of the common duct for many years, but it has not always been successful, the reason being that the tract is most often a tube of connective tissue, not lined with epithelium, and will probably continue to shrink. As time goes on there is danger that the condition will recur and lead to cyst formation, abscess or some other complication.

The secretion of the pancreas is necessary to life, and it is estimated that the amount secreted daily is about 400 cc. It is not, then, dehydration that kills the patient with a large fistula but a loss of the chemicals contained in the large amounts of secretion. So far the biochemists have not been able to supply substitutes for everything that the pancreas furnishes the organism, but they are on the way, and I think that soon it will be possible to remove the pancreas in toto for cancer and give the patient something as a substitute, unless Dr. Rowntree and his associates make all surgical treatment of cancer unnecessary.

The story of cancer of the pancreas is disheartening from a surgical standpoint, and the cysts, the traumas and the fistulas just about completed the series of successful surgical conditions until recently, when adenoma of the pancreas was brought to attention. If the medical workers and the chemists will do what surgeons require of them, I feel certain that with the younger investigators coming along the way they are, it will not be long before surgeons can do anything required with regard to the pancreas.

Dr. John J. Gilbride, Philadelphia: My experience in this regard has been limited to a study of a few of my own patients with pancreatic fistula, some patients seen through the courtesy of the late Dr. John B. Deaver, with whom I made the rounds of the wards for years at Lankenau Hospital, and some experimental work on dogs.

The management of pancreatic fistula is a difficult task. In these cases the course was violent, being characterized by severe local and systemic manifestations—local in the digestive effect on the abdominal wall and general in the effect caused by toxemia, dehydration and acidosis.

Treatment consists in the protection of the abdominal wall, administration of alkalis, milk diet and replacement of the body fluids.

Many of the cases of pancreatic fistula reported in the literature do not appear to me to be of this type, largely because of the mild and prolonged course, in some of them extending over a year or two. That is not the course of pancreatic fistula in my experience. According to what I have seen of so-called fistulous tracts in the human being, the wall is formed by the adjacent organ, and there is

not a definite, fibrous, separate-walled tract. Furthermore, in my opinion, it is absurd to speak of the transference of the wall of a fistulous tract. A fistula is controlled by attacking it at its source and not by attacking it at its termination; moreover, a fistulous tract will close of its own accord when its cause has been removed.

Dr. Rolf Lium, Boston: I have seen two patients with pancreatic fistula. One was in a man of 45 who had had local resection for carcinoma of the ampulla of Vater. Dr. Beth Vincent performed this operation, and in the course of the procedure the duct of Wirsung was cut across. A catheter was inserted into the duct, and brought out transduodenally and through the abdominal incision. In the eleven days following the operation it was possible to collect pure pancreatic juice, which varied in amount from 200 to 1,400 cc. in twenty-four hours. The latter figure is the largest amount of pancreatic secretion that has ever been obtained from the fistula of a human being.

The other patient was a boy with traumatic rupture of the pancreas. The pancreatic bed was drained after abdominal exploration, and a fistula became established which drained 500 cc. a day. He had several attacks of epigastric pain, nausea and vomiting, with tumor formation, all of which subsided on reestablishment of the fistula. When he entered the Lahey Clinic, four months after the original injury, he was placed on the Wohlgemuth regime. This produced a diminution in quantity of secretion to about 150 cc. a day; but once the reduction had been effected, the secretion remained at a plateau level and showed no evidence of further reduction.

Dr. Lahey performed a pancreatojejunostomy which was successful. Six months later the patient, while playing baseball, was again struck in the abdomen, and because of the severe pain another exploratory operation was performed. The line of anastomosis was perfectly intact, and definite injury was not demonstrated.

A pancreatic fistula arises after some types of surgical procedure in the neighborhood of the pancreas, and in 60 to 80 per cent of cases it follows marsupialization and drainage of a pancreatic cyst. This type of treatment has the sanction of long usage, but it is not the only method that has been tried. I have found reports by various authors of twelve cases in which primary anastomosis was effected between a pancreatic cyst and the digestive tract. In six cases pancreatogastrostomy was performed, in two cases each pancreatoduodenostomy and pancreatocholecystostomy and in one case pancreatojejunostomy. The operative mortality was zero, and all the patients were well after operation. One patient died of pulmonary tuberculosis seven weeks after operation, and the pancreatic cyst had shrunk from the size of a child's head to that of a walnut. No retrograde infection of the pancreas occurred.

In view of these cases I believe that primary anastomosis between a pancreatic cyst and the gastro-intestinal tract should be part of the surgical treatment of this condition. It will save the surgeon and the patient the trouble of a postoperative fistula, and in certain instances it will avoid a secondary operation for transplantation.

Dr. A. C. Ivy, Chicago: I should like to correct a statement made by the last speaker. Secretin has been injected intravenously into human beings by three other groups of workers, and it has been found to be active; as a matter of fact, it has been suggested by two different groups as a means of testing pancreatic function.

I have frequently been asked questions pertaining to the care of the patients with a pancreatic fistula, particularly in cases in which a great deal of digestion of the abdominal wall occurs. What can be done to decrease the production of pancreatic juice? I was interested in Dr. McCaughan's report primarily from the point of view of inhibitors of pancreatic secretion. I gathered, as I followed his slides, that according to his observations atropine is probably the best drug for that purpose. My colleagues and I have been giving the question considerable attention in our laboratory this past year, and Dr. Craft has found that ephedrine given subcutaneously is the best drug for reducing the pancreatic secretion in the dog; as a matter of fact, if 10 mg. of ephedrine is given subcutaneously every two hours, the pancreatic secretory response to a meal can be decreased by 50 per cent. We use silicon dioxide gel as a dressing powder. As to diet, the Wohlgemuth recommendation is the best, namely, a low carbohydrate, medium protein and high fat diet, with sodium bicarbonate.

DR. J. M. MCCAUGHAN, St. Louis: I agree with Dr. Lium's discussion of the principles of treatment in these cases.

I should like to show again a slide that I put on before demonstrating the resection of the distal third of this stomach. It might be expected, of course, that this resection would interfere with gastric motility, and also one might expect that the various substances when injected into the stomach would pass into the jejunum rather than into the duodenum and that the effect quantitatively and qualitatively on the pancreas might indeed be different. That is partly unanswerable. However, I believe that Dr. Ivy has done some work in which he has brought up a loop fistula in dogs, the so-called Thiry-Vella fistula, and has then applied to the jejunum some of the same substances, particularly mineral acids and fats. He has shown that when a transplant of the pancreas is made subcutaneously, secretion of pancreatic juice takes place when these materials are applied to the jejunum. As can be seen, such a transplant is entirely free from any nerve or vascular connection with the duodenum.

LIPOPENIA ASSOCIATED WITH CHOLESTEROL *ESTERSTURZ* IN PARENCHYMATOUS HEPATIC DISEASE

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AND
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In 1926 Thannhauser and Schaber,[1] developing the observation made by Feigl about eight years previously, found a considerable decrease in the ratio of ester to total cholesterol of blood in parenchymatous hepatic disease. To this phenomenon they gave the name cholesterol *Estersturz* and said they considered that it was due to impairment of the liver in a postulated synthesis of cholesterol esters.

Since that time controversy has arisen regarding not only the correctness of the interpretation but even the validity of the actual findings in the blood. Most of the clinical evidence pro and con has been reviewed by Gardner and Gainsborough [2] and by Epstein,[3] and the experimental angle has been discussed by Chanutin and Ludewig [4] in a paper which constitutes a valuable contribution to the subject. Much of the disparity in clinical observations and a good deal of the disparity even in the more controllable experimental work on animals have been due to the failure of investigators to take into account factors other than damage to the liver which affect the concentration of cholesterol bodies and other lipids in blood. One of the commonest of these other factors is fever, which has a definite lipopenic effect if of any duration

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1. Thannhauser, S. J., and Schaber, H.: Ueber die Beziehungen des Gleichgewichtes Cholesterin und Cholesterinester im Blut und Serum zur Leberfunction, Klin. Wchnschr. **5**:252-257, 1926.

2. Gardner, J. A., and Gainsborough, H.: Blood Cholesterol Studies in Biliary and Hepatic Disease, Quart. J. Med. **23**:465-483, 1930.

3. Epstein, E. Z.: Cholesterol of the Blood Plasma in Hepatic and Biliary Disease, Arch. Int. Med. **50**:203-222 (Aug.) 1932.

4. Chanutin, A., and Ludewig, S.: The Blood Plasma Cholesterol and Phospholipid Phosphorus in Rats Following Partial Hepatectomy and Following Ligation of the Bile Duct, J. Biol. Chem. **115**:1-14, 1936.

but which may be lipemic in its early stages.[5] The weight of available evidence indicates that in uncomplicated parenchymatous disease of the liver there occurs a decrease in plasma ester cholesterol, with variable changes in plasma-free cholesterol, and hence that there is a more significant decrease in the ratio of ester to total cholesterol. In uncomplicated obstructive jaundice, on the other hand, the common finding is hypercholesteremia. The determination of ester and total cholesterol has therefore been advocated, especially by Epstein,[3] as a diagnostic aid in differentiating obstructive from nonobstructive jaundice.

Gardner and Gainsborough [2] stated the opinion that the *Estersturz* is due to failure of absorption of cholesterol and fat from the intestine in the absence of bile, because they found a low ester—total cholesterol ratio in cases of biliary fistula. Hawkins and Wright [6] said they disagreed with this conclusion because they obtained a low ratio even though bile was present in the stools. Thannhauser and Schaber [1] originally postulated that the condition is due to failure of the liver to synthesize cholesterol esters at the normal rate.

Many of the interpretations of the changes in cholesterol metabolism are rendered futile by failure to consider cholesterol as an inherent part of lipid metabolism. Cholesterol binds with fatty acids to produce cholesterol esters, and these esters are undoubtedly under the influence of factors which affect lipid metabolism. Cholesterol admittedly may function beyond the realm of lipids, but this does not justify its isolation from lipids, as apparently implied by Gardner and Gainsborough [2] ("Cholesterol and its derivatives are too often lumped together with fats, lecithides, etc., with which they have not the slightest chemical connexion, under the misleading term 'lipoid.'"). In the present work it was found that the cholesterol *Estersturz* of parenchymatous hepatic disease was in reality part of a general lipopenia, a finding which must certainly be considered in evaluating any explanation.

The present work comprised a study of twenty-seven patients with nonobstructive jaundice or bilirubinemia from the medical divisions of the Kingston General Hospital. A variety of hepatic conditions was included in this group, such as hepatic cirrhosis, congestion of the liver, catarrhal jaundice, arsphenamine poisoning and hepatic toxemia of pregnancy (one case). All the patients exhibited in common bilirubinemia, with a plasma cholesterol *Estersturz* and no evidence of increased body temperature or any other condition apart from the hepatic disturbance which is known to affect the concentration of plasma lipids. Blood was obtained during fasting and oxalated. Extracts of the plasma and of the red blood cells were immediately prepared by the method of cold dilution, and the extracts were analyzed by a modification of the oxidative micromethods of Bloor, as used in previous studies.[5] The results obtained have been summarized statis-

5. Boyd, E. M.: The Lipopenia of Fever, Canad. M. A. J. **32**:500-506, 1935.

6. Hawkins, W. B., and Wright, A.: Blood Plasma Cholesterol: Fluctuations Due to Liver Injury and Bile Duct Obstruction, J. Exper. Med. **59**:427-439, 1934.

tically in tables 1 and 2, in which the values for normal adults are those previously obtained by these same methods.[7]

Accompanying the cholesterol *Estersturz* of hepatic disease there was found to be statistically significant lipopenia (table 1) analogous to the lipopenia of fever [5] and of hyperthyroidism.[8] The average values

TABLE 1.—*Lipopenic Changes in Plasma Associated with Cholesterol Estersturz in Parenchymatous Hepatic Disease*

Value	Composition of Total Lipid*						
	Total Lipid	Neutral Fat	Total Fatty Acid	Cholesterol			Phospholipid
				Total	Ester	Free	
Normal Adults							
Arithmetical mean	617	154	362	181	128	53	195
Standard deviation	75	77	62	22	23	10	37
Coefficient of variation	12	50	17	12	18	19	19
Adults with Parenchymatous Hepatic Disease							
Arithmetical mean	390	133	237	105	65	40	102
Standard deviation	59	68	45	21	22	11	33
Coefficient of variation	15	51	19	20	34	27	32
Average percentage decrease from normal	37	14	35	42	49	25	48
Mean subtracted from normal mean	227	21	125	76	63	13	93
Standard deviation plus normal standard deviation	134	145	107	43	45	21	70

* The lipid values are expressed in milligrams per hundred cubic centimeters of plasma.

TABLE 2.—*The Lipid Content of the Red Blood Cells in Parenchymatous Hepatic Disease Associated with Cholesterol Estersturz in Plasma*

Value	Composition of Total Lipid*						
	Total Lipid	Neutral Fat	Total Fatty Acid	Cholesterol			Phospholipid
				Total	Ester	Free	
Normal Adults							
Arithmetical mean	508	93	333	140	6	140	361
Standard deviation	62	42	41	32	9	26	56
Coefficient of variation	10	45	12	23	150	19	15
Adults with Parenchymatous Hepatic Disease							
Arithmetical mean	708	55	371	184	50	134	426
Standard deviation	152	52	78	53	51	15	87
Coefficient of variation	22	95	21	29	102	11	20

* The lipid values are expressed in milligrams per hundred cubic centimeters of red blood cells.

of lipids in plasma were decreased from 14 to 49 per cent. The most marked decrease was noted in the total and ester cholesterol and phospholipid values, all three of which were lowered by 40 to 50 per cent, on the average. The total lipid and total fatty acid values fell by a

7. Boyd, E. M.: The Lipemia of Pregnancy, J. Clin. Investigation **13**:347-363, 1934.

8. Boyd, E. M., and Connell, W. F.: The Lipopenia of Hyperthyroidism, Quart. J. Med. **6**:231-239, 1937.

mean of 30 to 40 per cent. Lesser average decreases were recorded in the concentrations of plasma neutral fat and free cholesterol, but these mean changes were not found to be statistically significant.

A statistically significant difference from normal in these results may be concluded to exist if the sum of the standard deviations of two corresponding means is less than the difference between the means. The differences between the means for plasma and the sum of the standard deviations of these same means are given in the last two lines of table 1. When the figure in the last line is less than the figure immediately above it, a significant change from normal may be concluded to have occurred in the concentration of that particular lipid. With this criterion of significance, there was found to be a real decrease in the total lipid, total fatty acid, total cholesterol, ester cholesterol and phospholipid contents of the plasma of these patients. There was not a significant decrease in the amount of free cholesterol and neutral fat. The data given in table 1 demonstrate just as clearly as if the results had been reported in toto that in parenchymatous hepatic disease associated with cholesterol *Estersturz,* many values for plasma neutral fat and free cholesterol may be found within as well as below the normal range but that practically all values for the other lipids of plasma are below the normal range.

To compare with normal the relative variations of lipid values in this type of hepatic disease, coefficients of variation have been calculated for each lipid. The coefficient of variation was determined by multiplying the standard deviation by 100 and dividing by the mean; it represents the standard deviation expressed as a percentage of the mean. The relative variation of the plasma total lipid, neutral fat and total fatty acid contents was about the same as normal, but there was 40 to 90 per cent more variation than normal in the values for the cholesterol fractions and phospholipid.

Coincident with the occurrence of lipopenic changes in the plasma, the lipid content of the red blood cells was found to be elevated in a number of instances, but this did not occur consistently enough to be labeled as statistically significant. These results are summarized in table 2. There were increases in the mean value of total lipid, total fatty acid, total cholesterol, ester cholesterol and phospholipid and a mean decrease in neutral fat and free cholesterol. In no instance was the sum of the standard deviations less than the difference of the means. This indicates that many of the values were within the normal range, which was precisely the case. As seen by the coefficients of variation, most of the values were considerably more variable than normal. It may be concluded that in parenchymatous hepatic disease with associated cholesterol *Estersturz,* instances occur in which there is an

increased lipid content of the red blood cells but that this does not occur in all or in a considerable majority of cases.

The results in one or two cases merit further discussion. A young man, a university student with a history of frequent occurrence of jaundice in his family, was admitted to the hospital with jaundice, grayish stools, slight fever and an icteric index of 30. The temperature rapidly subsided with recovery of the patient, and a few days later lipid analysis revealed 90 mg. per hundred cubic centimeters of free and no ester cholesterol in the plasma. The plasma phospholipid content was 52 mg. per hundred cubic centimeters, but the neutral fat value was markedly elevated, to 305 mg. per hundred cubic centimeters, and the plasma was distinctly milky. The nonoccurrence of ester cholesterol in human plasma has previously been reported [1] but is rare.

A second interesting case was that of a married woman (tripara) aged 24 with hepatic toxemia of pregnancy. No values for plasma lipids have previously been reported in this rare condition. The patient was eight months pregnant when admitted to the hospital. She had been vomiting regularly for nearly a month and was slightly jaundiced. She had vague pains in the legs, areas of paresthesia on the hands and exaggerated reflexes. The blood pressure was normal, and the urine contained 1+ albumin, acetone, diacetic acid, bile and a few casts. The blood showed an elevated urea content (46 to 66 mg. per hundred cubic centimeters), a low plasma albumin content (2.7 Gm. per hundred cubic centimeters) and an icteric index varying between 18 and 36, but normal dextrose and uric acid contents and a normal carbon dioxide-combining power. Analysis of the plasma revealed a total lipid content of only 413 mg. per hundred cubic centimeters, less than half that normally expected at this time, since the patient should have shown, if normal, lipemia of pregnancy.[7] The following values were noted: 68 mg. of neutral fat, 227 mg. of total fatty acid, 123 mg. of total cholesterol, 63 mg. of ester cholesterol, 60 mg. of free cholesterol and 180 mg. of phospholipid per hundred cubic centimeters of plasma. All these values are subnormal for a pregnant woman near term,[7] except the phospholipid and free cholesterol values, which were about what might be found normally. The case is of interest as being the first recorded instance of a complete differential lipid analysis of plasma in hepatic toxemia of pregnancy.

The next question for consideration concerns the interpretation that can reasonably be placed on these results in cases of parenchymatous disease of the liver. Gardner and Gainsborough,[2] from studies of cholesterol alone, said they considered that the decrease in plasma cholesterol esters was due to failure of proper absorption of cholesterol and fat from the intestine in the absence of bile. While Hawkins and

Wright [6] said they discounted this explanation with the finding of bile in the stool together with a low plasma ester value, the present results show further that this theory is untenable. One could scarcely conceive of impaired intestinal absorption simultaneously lowering the plasma content of cholesterol esters and phospholipid but having no effect on free cholesterol and neutral fat. During the absorption of sufficient quantities of fat by the intestine, all plasma lipids, especially neutral fat, are increased in value.

The original explanation of Thannhauser and Schaber,[1] that cholesterol esters are decreased in plasma because damage to hepatic cells hinders one of their functions in synthesizing esters from cholesterol and fatty acids, appears to be the most reasonable theory to account for the results. Cholesterol esters are not stored to any extent in normal tissues, although they are apparently synthesized as a by-product in degenerating tissue.[9] A lessened production of cholesterol esters would thus soon result in a diminution in their concentration in the plasma, the only medium in which they are found in any quantities. Thannhauser and Schaber [1] have argued that since damage to the liver lowers the plasma content of cholesterol esters, it is likely that these substances are produced in the liver. Supporting this is the fact that cholesterol esterases have been found in the liver.

The theory that hepatic damage is the cause of the decrease in plasma ester cholesterol is further substantiated by the fact that the same theory may be invoked to explain the decrease in phospholipid of plasma found herein and found experimentally by Chanutin and Ludewig.[4] The liver has been postulated by many, more recently by Sinclair,[10] as a probable site of the synthesis of phospholipids. Accepting this, it is reasonable to find that in parenchymatous hepatic disease the plasma content of phospholipid falls, since metabolic phospholipid is also not generally stored in other tissues of the body.[10]

It is generally accepted that cholesterol is readily synthesized in many tissues of the body. Neutral fat is present in abundance in practically all tissues of the body, being the storage form of fat. Damage to the liver would not therefore be expected to have any considerable effect on the concentration of either of these substances in plasma. Any decrease which does occur is probably due to the presence of insufficient phospholipid to aid in the colloidal solution of these aqueous insoluble substances.

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9. Boyd, E. M.: The Relation of Lipid Composition to Physiological Activity in the Ovaries of Pregnant and Pseudopregnant Rabbits, J. Biol. Chem. **108**:607-617, 1935.

10. Sinclair, R. G.: Fat Metabolism, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1937, vol. 6, pp. 245-268.

Assuming that a dynamic equilibrium exists between lipids in plasma and lipids in tissues, impairment of hepatic function would thus result in a gradual decrease in plasma phospholipid and cholesterol ester contents but would not necessarily affect the content of free cholesterol and of neutral fat. This appears to be the most likely explanation of the results obtained herein, but it is advanced as a working hypothesis, not as a proved theory.

A point which is difficult to bring into line with this hypothesis is the accumulation of fat and cholesterol esters in the liver in certain conditions (acute yellow atrophy, depancreatized insulinized dogs) in which the plasma content of cholesterol esters falls.[10] The latter cholesterol esters may represent esters produced as a result of degeneration, as in the ovary,[9] rather than metabolic esters, but why such esters do not readily diffuse into the plasma is a question. The fact that administration of choline and some related compounds relieves the fatty infiltration of the liver and brings the lipopenic plasma value to normal in experimental animals suggests that the synthesis of phospholipid and the synthesis of cholesterol esters in the liver may be in some manner interrelated.[10]

SUMMARY

A statistically significant decrease, averaging 35 to 49 per cent, was found in the concentrations of plasma total lipid, total fatty acid, total and ester cholesterol and phospholipid in twenty-seven cases of parenchymatous hepatic disease with associated cholesterol *Estersturz*. Lesser average decreases in the plasma neutral fat and the free cholesterol content were noted but were not found to be statistically significant.

Occasionally, increased amounts of lipid were encountered in the red blood cells, but in other cases the values were within the normal range, and there was no change in the red blood cells which was characteristic for the entire group.

A case in which there was no plasma ester cholesterol and a case of hepatic toxemia of pregnancy are reported.

STUDIES ON PORPHYRIA

III. ACUTE IDIOPATHIC PORPHYRIA

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The clinical and pathologic aspects of porphyria were extensively reviewed by Mason, Courville and Ziskind [1] in 1933. In the German literature the chemistry of porphyria has recently received considerable attention.[2] In the American literature recent papers by Dobriner and his associates,[3] Watson [4] and Watson and Clarke [5] have added important new data. The recent monograph by Waldenström [6] has clarified

From the University of Chicago Clinics, Chicago.

1. Mason, V. R.; Courville, C., and Ziskind, E.: Porphyrins in Human Disease, Medicine **12**:355, 1933.

2. (*a*) Fischer, H.: Ueber Hämin und Porphyrine, Verhandl. d. deutsch. Gesellsch. f. inn. Med., Kong. 45, 1933, p. 7. (*b*) Waldenström, J.: Some Observations on Acute Porphyria, Acta med. Scandinav. **83**:281, 1934; (*c*) Untersuchungen über Harnfarbstoffe, hauptsächlich Porphyrine, mittels der chromatographischen Analyse, Deutsches Arch. f. klin. Med. **178**:38, 1935. (*d*) Waldenström, J.; Fink, H., and Hoerburger, W.: Ueber ein neues bei der akuten Porphyrie regelmässig vorkommendes Uroporphyrin, Ztschr. f. physiol. Chem. **233**:1, 1935. (*e*) Schreus, H. T.: Ergebnisse und Probleme der Porphyrinforschung, Klin. Wchnschr. **13**:121, 1932.

3. (*a*) Dobriner, K.: Urinary Porphyrins in Disease, J. Biol. Chem. **113**:1, 1936; (*b*) Simultaneous Excretion of Coproporphyrin I and III in a Case of Chronic Porphyria, Proc. Soc. Exper. Biol. & Med. **35**:175, 1936. (*c*) Dobriner, K., and Rhoads, C. P.: The Excretion of Coproporphyrin I Following Hemorrhage in Dogs, J. Clin. Investigation **17**:105, 1938; (*d*) The Metabolism of Blood Pigments in Pernicious Anemia, ibid. **17**:95, 1938.

4. Watson, C. J.: Concerning the Naturally Occurring Porphyrins: I. The Isolation of Coproporphyrin I from the Urine in a Case of Cinchophen Cirrhosis, J. Clin. Investigation **14**:106, 1935; II. The Isolation of a Hitherto Undescribed Porphyrin Occurring with an Increased Amount of Coproporphyrin I in the Feces of a Case of Familial Hemolytic Jaundice, ibid. **14**:110, 1935; III. The Isolation of Coproporphyrin I from the Feces of Untreated Cases of Pernicious Anemia, ibid. **14**:116, 1935; IV. The Urinary Porphyrin in Lead Poisoning as Contrasted with That Excreted Normally and in Other Diseases, ibid. **15**:327, 1936; V. Porphyrins of the Feces, ibid. **16**:383, 1937.

5. Watson, C. J., and Clarke, W. O.: The Occurrence of Protoporphyrin in the Reticulocytes, Proc. Soc. Exper. Biol. & Med. **36**:65, 1937.

6. Waldenström, J.: Studien über Porphyrine, Acta med. Scandinav., 1937, supp. 82.

the diagnostic criteria, the familial occurrence and much of the symptomatology of acute porphyria. The first two papers of the present series of studies [7] have further introduced the basic chemical nature of the porphyrins and have presented evidence that porphyria may be a persistence of fetal pyrrole metabolism. For these reasons it is not considered necessary in this paper to go deeply into either the clinical or the chemical aspects that have been dealt with in the literature.

The present report of a case concerns what is commonly called acute idiopathic porphyria. Fischer and Libowitzky [8] have recently reported the first case of acute toxic porphyria with excretion of uroporporphyrin I, but the present case is the first one in which this porphyrin has been found in the idiopathic type of the disease. Evidence is presented that the metabolic disturbance is not limited to the period of acute symptoms. The persistence of this metabolic error between attacks and its familial occurrence suggest that acute idiopathic porphyria may be as much an inborn error of pyrrole metabolism as is congenital porphyria.

REPORT OF A CASE

Mrs. E. D., aged 29, a graduate nurse employed in a pediatric hospital, was admitted to the hospital on June 25, 1935.

Complaint.—The patient complained of unbearable pains in the head, abdomen, back and extremities, which had been felt for three days.

History of the Present Illness.—The exact date of onset of the illness was uncertain. In 1931 pains in the right lower quadrant of the abdomen led to appendectomy. Since 1932 she had suffered from increasing constipation and insomnia. Examination of the blood in 1931 revealed an erythrocyte count of 4,510,000, the hemoglobin value being 90 per cent (Sahli). In 1932, for some reason, a blood count was made, and it showed an erythrocyte count of 4,700,000, with a hemoglobin value of 70 per cent (Sahli). One month later the hemoglobin value (Sahli) was 65 per cent. The patient was given iron and was irradiated with a quartz mercury vapor arc lamp. In two months the hemoglobin value rose to 78 per cent (Sahli), and a dark tan developed. About this time she was told that she was jaundiced, but she paid no attention to it.

On June 16, 1935, she was married. The honeymoon was uneventful. About June 18 she used a douche of saponated solution of cresol. No other drug, medication or alcohol was used at this time. The evening before her marriage she took an enema of tap water. This produced the last defecation until June 30, fifteen days later. On June 21 she began having headache, with nausea and retching. This persisted and became more severe, with vomiting and abdominal cramps.

7. (*a*) Turner, W. J.: Studies on Porphyria: I. Observation on the Fox Squirrel, Sciurus Niger, J. Biol. Chem. **118**:519, 1937. (*b*) Turner, W. J., and Obermayer, M. E.: Studies on Porphyria: II. A Case of Porphyria Accompanied with Epidermolysis Bullosa, Hypertrichosis and Melanosis, Arch. Dermat. & Syph. **37**:549 (April) 1938.

8. Fischer, H., and Libowitzky, H. L.: Auftreten von Urò-bzw. Koproporphyrin I bei klinischer Porphyrie, Ztschr. f. physiol. Chem. **241**:220, 1936.

Pains spread to the extremities, and after a "fainting spell" on June 25 she was brought to the hospital.

Past History.—Except for urticaria when a child the patient had always been healthy, active and sociable. For several winters she had suffered from recurrent sinusitis, for which she had used acetphenetidin in small amounts. The last dose of this was taken in December 1934. No other drugs had been taken, and no history of contact with lead could be elicited. In 1930 her blood pressure was recorded as 110 systolic and 80 diastolic. The genito-urinary history revealed no abnormality except moderate dysmenorrhea. She had never noted the color of her urine.

Family History.—The data for the patient's family are given in the accompanying diagram.

There is no history of consanguinity in the antecedents of the patient. No member of the family was known to have had a cutaneous eruption. The patient's mother died of carcinoma of the breast.

Specimens of urine from all the living members of the family (twenty-eight) were examined. Only in the urine of the patient and that of her eldest sister

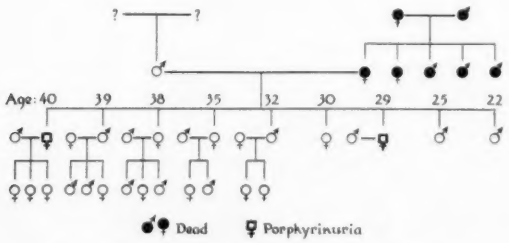

Chart giving the data for the patient's family.

was uroporphyrin found. There was no opportunity for direct examination of this sister, so it is not known whether or not she had porphyrinopathic symptoms.

Physical Examination.—The temperature was 99.4 F., the pulse rate 104, the respiratory rate 24 and the blood pressure 160 systolic and 90 diastolic.

The patient appeared critically ill. She was admitted to the gynecologic service. Although the abdomen was soft, tubal abortion was suspected. The patient was prepared for examination under anesthesia. During the preparation she had two epileptiform convulsions lasting several minutes each, followed by coma of from five to ten minutes. With the patient under ethylene anesthesia no pelvic mass could be found, and operation was deferred.

When the patient was returned to her room the blood pressure was 180 systolic and 100 diastolic. At this time a more complete physical examination was made. It was noted that the complexion was strikingly dirty gray-yellow, with cyanosis of the lips. Between convulsions the patient was too restless for satisfactory examination, but it was seen that the pupils were small, round and equal and reacted well to light. She was able to see, but she failed to recognize old friends. During convulsions the pupils dilated equally and did not react to light. The fundi revealed pallor, but it could not be ascertained whether there was vascular constriction.

The lungs were clear and resonant.

The radial pulse was equal on the two sides, of bounding type and of high tension. The rhythm was regular. There were no murmurs over the heart, and the heart was not enlarged.

The abdomen was soft. There were no palpable masses.

The convulsions were typically epileptiform, with simultaneous loss of consciousness and generalized tonic spasms, opisthotonos, cessation of respiration and mydriasis. There was, however, neither defecation nor urination. From the appearance of the patient, who seemed more markedly excited just before loss of consciousness, it was thought probable that there was an aura. The duration of the attacks was from one to five minutes. As the tonic spasm passed the patient relaxed into coma without having a phase of clonic movements. The coma persisted for from a few minutes to half an hour. In the period of wakefulness she rolled and tossed in bed, oblivious to the presence of others unless she was touched or addressed. She would answer questions, but only after a delay and then often irrelevantly.

She complained bitterly of pains in the abdomen, head, back and extremities and seemed not to find relief in any position. Phenobarbital, scopolamine hydrobromide and morphine were ineffectual.

Course in the Hospital.—On the night of entry the patient voided a small amount of urine, reported as being red-brown, with a trace of albumin and a few hyaline casts but no red blood cells. The leukocyte count was 12,200. During a convulsion lumbar puncture was performed, revealing clear fluid under no increase of pressure, with no cells and no increased content of protein. Lumbar puncture two days later also gave normal results.

June 26: The temperature reached 101 F. by rectum. The pulse rate was persistently about 120, with a blood pressure of 178 systolic and 110 diastolic. There was another convulsion during the night.

June 27: The dusky green cyanosis was more impressive than before. The patient slept most of the time but could be aroused without much difficulty. She answered questions slowly and incompletely. Toward noon she began to grow restless and to roll around in bed. At 1:55 p. m. she had a convulsion beginning in the left arm and quickly spreading to the right. This lasted about two minutes and was followed by sleep. A few moments later there was a similar attack. The rest of the day convulsions recurred about every ninety minutes, beginning in the left thumb, ascending the arm and then crossing to the right sternocleidomastoid muscle. In some attacks the muscles of the left thigh showed clonic contractions. The patient seemed semistuporous for the first part of each attack but soon became comatose. About 6:15 p. m. she became restless and cried out. After 0.09 Gm. of phenobarbital was given she became quiet, and the convulsions ceased.

On this day the urine was dark red-brown, of such a striking hue as to suggest the presence of melanin. Suspicion of porphyria was aroused, but spectroscopic examination of the urine showed only a diffuse absorption in the blue-violet region.

June 28: The patient looked much better and was able to take liquids. The temperature remained between 100 and 101.8 F., and the pulse rate, between 120 and 130. The blood pressure fluctuated between 180 systolic and 112 diastolic and 158 systolic and 112 diastolic. The morning urine was light yellow but became darker on exposure to light.

June 30: The patient was rational and coherent, but her speech was slurred and slow. There was rapid nystagmus on looking to the right or left or upward, and there was complaint of blurring of vision. The fundi were normal. Weakness of the left side of the face and definite ataxia and dysdiadokokinesis of the left hand were noted.

The daily urinary output, which had been between 250 and 850 cc., suddenly increased to 1,870 cc., and the evening blood pressure fell to 146 systolic and 100 diastolic. The temperature remained between 100 and 102 F., with a persistently fast pulse rate. The leukocyte count was 11,500, and the erythrocytes numbered 5,160,000 per cubic millimeter.

July 2: Severe pain continued. She was given 10 cc. of a 10 per cent solution of calcium gluconate intravenously, with immediate and striking relief. This was of short duration but could be obtained on each repeated injection. The following day she went to sleep during an injection given for pain and restlessness.

July 15: The patient complained that pains were present in the right arm. At this time the diagnosis of porphyria was verified by spectroscopic demonstration of porphyrins in the fresh, light yellow morning urine. After standing the urine turned dark, and the porphyrin spectrum was obscured.

July 24: The patient awoke with paralysis of the right ulnar and radial nerves. After this she improved rapidly. The paralysis cleared quickly.

August 13: The patient left the hospital on the forty-ninth day after entry.

Laboratory Examinations.—The Wassermann and Kahn tests were carried out on the blood and spinal fluid and gave negative reactions.

The leukocyte count remained elevated at least until July 20, with a peak of 18,800 on June 29. The differential counts usually showed about 86 per cent neutrophils, 10 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils. On June 26 the hemoglobin value was 92 per cent (Sahli) and the erythrocyte count 5,010,000. The nonprotein nitrogen content was 33 mg., and the dextrose content was 155 mg. per hundred cubic centimeters. On June 29 the nonprotein nitrogen content was 19 mg. and the dextrose content 102 mg. On July 8 the dextrose content was 71 mg., the average normal value for the method. The calcium content was 9.9 mg. per hundred cubic centimeters. A special hematologic report on July 10 showed: hemoglobin, 85 per cent (Newcomer); erythrocytes, 4,800,000 per cubic millimeter; leukocytes, 10,250; platelets, 340,000; neutrophils, 69 per cent; lymphocytes, 23 per cent; monocytes, 7 per cent, and eosinophils, 1 per cent. On July 27 the reticulocyte value was 0.8 per cent, and the smear was normal. The following day the reticulocytes numbered 1 per cent. The fragility test gave a normal result. The coagulation time was two and one-half minutes; the patient did not bleed.

Roentgenograms, made on June 25, showed marked gaseous distention of both large and small intestine. There was no evidence of a stone in the urinary tract. Complete roentgenologic examination of the spine, long bones and bones of the hands and wrists showed no abnormality.

Stools were examined twice. The first specimens were brown scybala which gave a negative reaction to the benzidine test. The second specimens were similar but were covered with a slight deposit of mucus.

Later Course.—Improvement continued, and the patient returned to work. The blood pressure returned to normal and remained there. The skin lost its dirty green cyanotic appearance, but small hard nodules developed deep in the epidermis, with no subjective symptoms. They did not break down but often became infected, clearing up in about a week without scarring. New ones have continued to appear at intervals up to the present. They are apparently intracutaneous cysts.

As the cyanosis disappeared it became evident that the patient had a yellowish pallor, but no test for bilirubinemia was made until December 5. At this time the bilirubin value was 2 mg. per hundred cubic centimeters, with an indirect van den Bergh reaction. Meanwhile it had been learned that the patient was excreting in the urine a substance giving a strong positive reaction to aldehyde

(Ehrlich). This will be considered later. On Jan. 3, 1936, a galactose test was made simultaneously with a bilirubin tolerance test. The former showed only a trace of reducing substance excreted in the first hour. For the latter, 46 mg. of bilirubin was injected intravenously. Before the injection the bilirubin value was 1.3 mg. per hundred cubic centimeters. It was 2.3 mg. after thirty minutes, 2.27 mg. after one hour, 2.06 mg. after three hours and 1.64 mg. after five hours. Normally this method shows total removal of excess bilirubin in four hours.[9]

From Nov. 24 to 26, 1935, generalized edema developed. The eyelids became swollen, and the patient had difficulty in putting on her shoes. With the onset of the catamenia on November 26, the knees also became greatly swollen. She had shooting pains in the face and arms. The flow stopped on November 30, and the symptoms abated.

On December 4 physical examination revealed the following: The skin was definitely jaundiced. Intracutaneous nodules were present on the nape of the neck, forehead and cheeks. The areolae of the nipples were large and dark brown. There was no hypertrichosis. The blood pressure was 116 systolic and 70 diastolic. Neurologically there was found only weakness of the hands.

On December 16 the blood was again examined. The hemoglobin value, as determined by the Van Slyke oxygen-combining method, was 14.96 Gm. per hundred cubic centimeters. For the same sample of venous blood the erythrocyte count was 4,800,000. The volume of packed red blood cells, determined by the Wintrobe method,[10] was 46.5 cc. per hundred cubic centimeters, corrected. The mean corpuscular volume was 97 cubic microns; the mean corpuscular hemoglobin value, 31 micromicrograms, and the mean corpuscular hemoglobin concentration, 31 per cent. The mean corpuscular hemoglobin value was at the upper limit of normal; that for the mean corpuscular volume was definitely above normal.[11] Examination of the blood smears revealed nothing abnormal. The leukocyte count was 7,200, with 45 per cent neutrophils, 50 per cent lymphocytes, 3 per cent monocytes and 2 per cent eosinophils. Fluorescent erythrocytes were not found in fresh unfixed, unstained smears.[12] The apparatus used has been previously described.[7a]

The blood serum contained no methemoglobin. Attempts to demonstrate porphyrin in serum by direct spectroscopic examination or by the Fischer acetic acid-ether method[13] failed. Hematin could not be detected spectroscopically by means of the cyanhemochromogen method in a 4 cm. depth of serum.

The patient was given a diet high in carbohydrate, without obvious effect. In the last few weeks of February 1936 she complained of pain in the interscapular region, particularly on the right side. By that time the jaundice had disappeared.

On May 21, 1936, she again began to have abdominal pain and felt tired, and she reentered the hospital on May 28. In this attack, which was milder than the first,

9. Harrop, G. A., Jr., and Barron, E. S. G.: The Excretion of Intravenously Injected Bilirubin as a Test of Liver Function, J. Clin. Investigation **9**:577, 1931.

10. Wintrobe, M. M.: The Size and Hemoglobin Content of the Erythrocyte, J. Lab. & Clin. Med. **17**:899, 1932.

11. Wintrobe, M. M.: Anemia: Classification and Treatment on the Basis of Differences in the Average Volume and Hemoglobin Content of the Red Corpuscles, Arch. Int. Med. **54**:256 (Aug.) 1934.

12. Keller, J., and Seggel, K. A.: Ueber das Vorkommen fluorescierender Erythrocyten, Folia haemat. **52**:241, 1934. Watson and Clarke.[5]

13. Fischer, H., and Schneller, K.: Zur Kenntnis der natürlichen Porphyrine: VI. Verbreitung des Porphyrins in Organen, Ztschr. f. physiol. Chem. **135**:253, 1924.

she became stuporous and complained chiefly of pain. Three weeks after the onset she suddenly had one convulsion, which was mild. Two days later she suddenly improved, and within a few days she was able to leave the hospital.

Since then she has been well, with a feeling of only moderate tiredness while at work. There is no more jaundice. The urine continues to contain the substance giving a positive reaction to aldehyde (Ehrlich) and still has an excessive amount of porphyrins. The uroporphyrin band at 6,140 angstroms is persistently visible in the fresh urine.

Chemical Studies.—During the first acute attack the studies of the urine were limited, and the stools were not examined. A small amount of ether-soluble porphyrin could be found in the urine. The urine was usually light yellow, but on oxidation it became dark red and the porphyrin spectrum was obscured. The chromogen failed to yield the pigment when treatment with nitrous acid preceded oxidation in light and air. This is in sharp contrast to the urorosein chromogen.[14]

In the interval between the first and the second attack, repeated studies of the urine and feces were made.

The first examination of stool was carried out by Dr. Konrad Dobriner, who reported such striking paucity of coproporphyrin that its demonstration depended on the use of fluorescence. I later corroborated this finding and also found large amounts of copromesobiliviolin in the feces.

Since there has been some suspicion that the dark color of the urine in cases of acute porphyria may be due to urorosein or some similar skatole or indole derivative,[15] a liter of fresh yellow urine was once acidified with sulfuric acid and subjected to steam distillation. The distillate showed a weak violet with Ehrlich's aldehyde reagent. It was obvious that this could not account for the intense pigmentation of the urine.

It was learned early that the patient's urine gave a strongly positive reaction to aldehyde (Ehrlich), the red solution showing the following absorption spectrum: I, 572 to 560 (maximum, 565) millimicrons; II, 510 to 488 millimicrons. These and subsequent measurements were made with a Zeiss model C hand spectroscope. On standing the solution became more brownish, the second band becoming stronger. With hydrochloric acid alone the urine turned red-brown, without the appearance of the band at 565 millimicrons. In contrast to this the urine of a patient with advanced cirrhosis of the liver gave a reaction with the following absorption spectrum: I, 560 to 550 (maximum, 555) millimicrons; II, 510 to 488 millimicrons. It seemed likely therefore that at least part of the former reactor was not urobilinogen. This was further corrborated by its insolubility in purified petroleum (petroleum ether) in which urobilinogen is easily soluble.[16] Waldenström [17] has noted much the same phenomenon. Further, Watson [18] has recently

14. Herter, C. A.: The Relation of Nitrifying Bacteria to the Urorosein Reaction of Nencki and Sieber, J. Biol. Chem. **4**:238, 1908; On Indolacetic Acid as the Chromogen of the "Urorosein" of the Urine, ibid. **4**:253, 1908.

15. Gutstein, M.: Fall von Nephroroseinurie, Ztschr. f. klin. Med. **43**:324, 1917. Maasse, C.: Auftreten von Skatolfarbstoff im Harn bei Hämatoporphyrie, ibid. **99**:270, 1924. Waldenström.[6]

16. Watson, C. J.: The Average Daily Elimination of Urobilinogen in Health and in Disease, with Especial Reference to Pernicious Anemia, Arch. Int. Med. **47**:698 (May) 1931.

17. Waldenström.[2c, 6]

18. Watson, C. J.: Studies of Urobilinogen: II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, Arch. Int. Med. **59**:196 (Feb.) 1937.

reported that in some instances urobilinogen-containing urine of patients with hepatic disease gave much the same results.

Toward the end of November 1935, 14 liters of urine was collected, acidified with acetic acid and allowed to stand open to the air beneath the hood for the development of color and the precipitation of porphyrins. This urine was filtered, and the filtrate was saved for later study.

The precipitate was found to consist largely of dark brown pigment, which obscured much of the porphyrin spectrum when in solution in ammonium hydroxide. This surprising phenomenon has not previously been reported. The pigments were insoluble in acetic or dilute hydrochloric acid but went readily into solution with dilute ammonium hydroxide. Reprecipitation by addition of acetic acid did not separate the porphyrins and the brown pigment. There was a trace of ether-soluble porphyrin, which was not further purified. Precipitation by Garrod's method with calcium hydroxide brought down most of the pigment, but covering with sulfuric acid-methyl alcohol and centrifugation caused the porphyrin to come out, leaving the brown pigment behind.

The porphyrin was esterified in the acid alcohol, taken into chloroform and purified in the usual way. After several recrystallizations in chloroform the maxima for the absorption spectrum, measured in a spectrophotometer, were: I, 626; II, 578; III, 538; IV, 502 millimicrons.[19] The crystals were sent to Prof. Hans Fischer, and his colleague Dr. Libowitzky reported:

"The 6 mg. of porphyrin ester showed fine bent recrystallized needles. The melting point was from 275 to 278 C., after sintering at 261 C. The mother liquor clearly contained coproporphyrin. The entire amount was heated with 1 per cent hydrochloric acid to 190 C. in a closed vessel for three hours, whereby the ester was saponified and decarboxylated. The resulting coproporphyrin was esterified after purification by the ether-hydrochloric acid method, and the ester crystallized. The crystals obtained sufficed for determination of the melting point at 241 to 242 C. Therefore, copro- I ester, or originally uro- I ester, was present, which is surprising in view of the clinical history. According to Waldenström, uroporphyrin III, which is typical of acute porphyria, was to have been expected."

The first filtrate of urine mentioned was then subjected to chromatographic analysis according to the method of Waldenström,[2e] the purest aluminum oxide powder being used, with a 1,000 cc. cylindric separatory funnel holding the column of powder. The substances obtained by elutions with 20 per cent acetic acid, glacial acetic acid, distilled water and 12 per cent ammonium hydroxide were separately collected. The first of these was not further studied. Elution with glacial acetic acid yielded, in addition to a large amount of dark brown pigment (urofuscin), a quantity of metal-porphyrin complex with the following absorption spectrum in glacial acetic acid: I, 565 to 550 (maximum, 557) millimicrons; II, 548 to 525 (maximum, 538) millimicrons. Elution with distilled water also brought down some metal complex.

Elution with ammonium hydroxide yielded a dark red solution rich in porphyrins. It was evaporated to about one-fifth its original volume, acetic acid was added and repeated extraction with ether was carried out. There was very little ether-soluble porphyrin, and this was not further purified. The aqueous phase was then adsorbed on a column of talc, which had been recommended by Waldenström [2e] as being superior to aluminum oxide for final purification of porphyrins by chromatographic analysis.

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19. The spectrophotometer manufactured by Bausch & Lomb Optical Company, Rochester, N. Y., was used.

The pigment remained limited to the upper half of the column, rendering it a pure red. The brown pigment with which it had been associated passed through, being completely removed by elution with glacial acetic acid. Some metal complex was also found in the glacial acetic acid.

The solution obtained from the talc by elution with ammonium hydroxide was a bright cherry red and showed the following spectrum: I, 570 millimicrons; shadow to 565 to 555 (maximum, 560) millimicrons; II, 540 to 525 (maximum, 530) millimicrons (order of intensity of bands: I, II). After addition of acetic acid the following spectrum was obtained: I, 575 to 565 (maximum, 570) millimicrons; II, 540 to 530 (maximum, 535) millimicrons (order of intensity; I, II). With 25 per cent hydrochloric acid the following spectrum was obtained: I, very weak, about 585 millimicrons; II, fine and weak, 552 millimicrons (order of intensity: II, I). After extraction from 25 per cent hydrochloric acid with amyl alcohol, the following absorption was noted in the alcohol: I, 565 millimicrons; II, about 535 to 525 millimicrons (order of intensity: I, II). This pigment was removed from amyl alcohol by tenth-normal potassium bicarbonate, in which the absorption was: I, 565 millimicrons; II, 535 to 530 millimicrons.

The addition of acid led to the precipitation of the pigment, which was filtered off, taken into 5 per cent ammonium hydroxide and reprecipitated. This time an astonishing fact was noted: The greater part of the pigment, a metal complex, remained in solution at p_H 3.4. This was sent to Dr. C. J. Watson for study The precipitate was insoluble in pyridine, but on addition of water it formed a bright red solution with the following absorption: I, 595 to 575 (maximum, 580) millimicrons; II, 550 to 530 (maximum, 538) millimicrons. Within a few minutes this had changed, band I moving to a maximum at 592 millimicrons, band II disappearing and a new band coming in at 630 millimicrons. With this, another appeared at about 500 to 490 millimicrons. On addition of a few drops of dilute ammonium hydroxide the absorption was: I, very fine, 605 millimicrons; II, 585 to 575 millimicrons, followed by diffuse absorption in the green and extinction at about 500 millimicrons. On addition of acetic acid the absorption changed to: I, 630 millimicrons; II, asymmetrical, 605 to 590 (maximum, 600) millimicrons (order of intensity: II, I). After twenty-four hours a precipitate formed and was filtered off. A test portion of this precipitate dissolved in pyridine showed the following absorption: I, about 610 millimicrons; II, very intense, asymmetrical, 580 to 560 (maximum, 565) millimicrons; III, intense, 535 to 525 (maximum, 530) millimicrons; IV, 505 to 480 (maximum, 490) millimicrons.

The remainder of the precipitate was covered with 2 per cent sulfuric acid-methyl alcohol and set aside to esterify. The violet solution was filtered off, leaving a red residue on the filter paper. The violet solution was added to a small volume of chloroform, water was then added and the chloroform solution of the pigment was washed with dilute sodium bicarbonate and evaporated to dryness in vacuo. Redissolved in chloroform it showed the following absorption: I, 625; II, 570; III, 535; IV, 500 millimicrons (spectrophotometric maxima). These are identical with those of uroporphyrin.[20] The previously mentioned insoluble red residue was dissolved in chloroform and washed according to the method described. It then had the following spectrum in chloroform: I, 585 millimicrons, shadow to 570 to 555 (maximum, 562) millimicrons; II, 535 to 518 (maximum, 530) millimicrons (order of intensity: I, II).

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20. Maurer, H.: Tierische Farbstoffe und synthetische Porphyrine, in Abderhalden, E.: Biochemisches Handlexikon, Berlin, Urban & Schwarzenberg, 1933, vol. 7, pp. 605-766.

The evidence thus far pointed to the occurrence of uroporphyrin I, together with a larger amount of metal-porphyrin complexes of the type of turacin.[21] The metal or metals in these complexes were not identified. With this was excreted one or more chromogens, giving rise to the red-brown of the urine. One of these chromogens gave a positive reaction to aldehyde (Ehrlich). Little coproporphyrin could be found either in urine or in feces. The porphyrins did not accumulate in the blood stream but were easily excreted. There was evidence of hepatic damage, apparently involving more of the excretory function than of the metabolic. There was evidence of slight macrocytic erythropoiesis.

It was thought desirable to repeat this study during the patient's second attack, wherefore 4 liters of urine was collected for study.[22] This time it was found that uroporphyrin I (melting point, 292 C., uncorrected) was excreted in considerably greater amount than were metal complexes. After the publication of Waldenström's monograph [6] the uroporphyrin from the mother liquors of the uroporphyrin I crystallizations was reexamined. It was then found that a considerable amount of uroporphyrin could be separated which had a noticeable solubility in absolute methyl alcohol. Comparison of two solutions of uroporphyrin, the one containing pure uroporphyrin I from Hans Fischer and the other from the mother liquors previously mentioned, revealed a marked difference in the solubility of the porphyrins on addition of methyl alcohol. That of the pure uroporphyrin I was negligible; the other left a bright red solution. Evaporation of this solution to small volume and cooling to —10 F. gave a small yield of fine cystals arranged in burrs. The yield was too small for a determination of the melting point, but the spectrum in chloroform was that of uroporphyrin.

Further studies of urofuscin were made and agreed in essence with the former.

COMMENT

It is evident that the acute attacks from which the patient suffered were exacerbations of a chronic condition. A review of the literature reveals this to be almost invariably so. In this connection Waldenström's [6] monograph is most instructive. One of his patients has had porphyria for more than a quarter of a century without experiencing an acute attack.[2b]

Aside from the familial occurrence in Sweden, which Waldenström's data indicated to be transmitted as a dominant mendelian characteristic, nine families, including that of the present patient, have been known to have more than one member with porphyria.[23]

21. Fischer, H., and Hilger, J.: Zur Kenntnis der natürlichen Porphyrine: VIII. Ueber das Vorkommen von Uroporphyrin (als Kupfersalz, Turacin) in den Turakusvögeln und den Nachweis von Koproporphyrin in der Hefe, Ztschr. f. physiol. Chem. **138**:49, 1924.

22. This part of the work was assisted by a grant from the Committee on Scientific Research of the American Medical Association.

23. van Berckel, G. J. J.: Porphyreën en Porphyrinen, Geneesk. bl. u. klin. en lab. v. d. prakt. **25**:1, 1926. Larjanko, J.: Klinische-pathologische Untersuchungen über die Porphyria idiopathica abdominalis, Acta Soc. med. fenn. duodecim **21**:1, 1935. Mason, V. R.: Personal communication to the author. Micheli, F.,

(Footnote continued on next page)

According to Waldenström,[6] the criterion for the diagnosis of porphyria is the demonstration of uroporphyrin in the urine. In congenital porphyria, with dermal manifestations, uroporphyrin I is the main type excreted, with a small amount of uroporphyrin III.[8] In acute porphyria type III preponderates. In addition there is excreted in cases of acute porphyria a substance which gives a positive reaction to aldehyde (Ehrlich). Waldenström[6] distinguished this from urofuscinogen, which gives a brownish pigment, stating that the aldehyde reactor yields a red substance on oxidation. Further, he identified this chromogen with a substance which gives a positive diazo reaction (Ehrlich). There appears to be still another characteristic of acute porphyria —the excretion of metal complexes. Waldenström[2e] mentioned it as occurring in the eluate of pigment from aluminum oxide by distilled water. It occurred in the present case. It has been noted in the porphyria of the fox squirrel.[7a] Whether it might be an artefact due to contamination by metals and subsequent complex formation must remain an open question at present.

The significance of uroporphyrin is unknown. To me it seems plausible that uroporphyrins are formed in the bone marrow from pyrromethenes brought from the liver by the blood stream.[24] It is possible that the coproporphyrins arise by decarboxylation of the uroporphyrins, for Dobriner and his associates[3] have shown that coproporphyrin excretion may be taken as an index of bone marrow activity. It is also possible that protoporphyrin is a product of still further decarboxylation of uroporphyrin.

Therapeutically there is relatively little that can be done for the patient with porphyria. Liver therapy is of little or no avail.[25] Indeed, Dobriner[26] has shown that although excretion of porphyrin in acute and congenital porphyria may be diminished by liver therapy, the excre-

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and Dominici, G.: Ueber zwei Fälle von familiärer Porphyrie mit letalem Ausgang, Deutsches Arch. f. klin. Med. **171**:154, 1931. Barker, L. F., and Estes, W. L.: Family Hematoporphyrinuria and Its Association with Chronic Gastro-Intestinal Dilatation, Peculiar Fits and Acute Polyneuritis, J. A. M. A. **59**:718 (Aug. 31) 1912. Ehrenberg, L.: Zur Kasuistik der mit Landryscher Lähmung einhergehenden Porphyrinuria, Klin. Wchnschr. **2**:1508 (Aug. 6) 1923. Schölberg, H. A.: An Undescribed Purple Pigment in the Urine, Tr. Path. Soc. London **53**:279, 1902. Maugeri, S.: Porfirinuria familiare e porfiria idiopatica, Riforma med. **52**:919, 1936.

24. Borst, M., and Königsdorffer, H.: Untersuchungen über Porphyrie mit besonderer Berücksichtigung der Porphyria congenita, Leipzig, S. Hirzel, 1929. Dobriner and Rhoads.[3d]

25. Waldenström.[6] Turner and Obermayer.[7b]

26. Dobriner, K.: Discussion at the Pediatric Session of the Southern Medical Society, Baltimore, Nov. 17, 1936, after presentation of two patients with porphyria by Dr. Harriet M. Guild. A report of these cases has not yet been published.

tion of uroporphyrin is not stopped. During the acute attack calcium therapy is effective for the relief of pain,[27] but whether it affects the ultimate outcome of an attack is uncertain.

SUMMARY

A patient with acute idiopathic porphyria with symptoms of lead poisoning excreted large amounts of a red-brown pigment complex called urofuscin. With this there were excreted also a small amount of uroporphyrin I and probably uroporphyrin III, together with considerable amounts of an unidentified metal complex. In the interval between attacks there was a larger amount of metal complex excreted than of porphyrin; during an attack this relation was reversed.

The hypertension noted during an attack disappeared as the symptoms abated.

During the interval between symptoms there were persistent excretion of urofuscin and evidence of hepatic disease.

The evidence points to the conclusion that acute idiopathic porphyria is actually a chronic metabolic disturbance. The familial occurrence of the condition substantiates the thesis that acute idiopathic porphyria is an inherited inborn error of metabolism.

Chemical studies of the blood and urine are reported which suggest the presence of hepatic damage, with bilirubinemia but little urobilinogenuria. The strong positive reaction of the urine to aldehyde (Ehrlich) was shown to be due to a chromogen, probably not urobilinogen.

It is suggested that uroporphyrins are formed in the bone marrow as the primary porphyrin complex, from which the coproporphyrins and protoporphyrin arise by decarboxylation.

CONCLUSIONS

Acute idiopathic porphyria may be associated with excretion of uroporphyrin I in excess of uroporphyrin III.

Excretion of metal-porphyrin complexes appears to be characteristic of acute idiopathic porphyria.

Most of the color of the urine in acute idiopathic porphyria is usually due to the presence of pigments which have been called urofuscin.

Acute idiopathic porphyria is a familial disease, probably inherited as a dominant mendelian characteristic.

The acute manifestations are alleviated by intravenous calcium therapy.

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27. Hoergurber, W., and Fink, H.: Ueber Porphyrine bei klinischer Porphyrie, Ztschr. f. physiol. Chem. **236**:136, 1935. Waldenström.[2d] Fischer and Libowitzky.[8]

GASTRIC SECRETION IN MAN

OBSERVATIONS ON THE EFFECTS OF REPEATED INJECTIONS OF HISTAMINE AND ON TRANSIENT ACHLORHYDRIA

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The following report is based on studies carried out on a trained subject for four and a half years. The subject was originally selected to serve as the source of gastric juice for patients with pernicious anemia. Because of the fact that he was receiving repeated injections of histamine, we decided to study his gastric secretion. At first attention was paid only to the volume and the acidity; later, determinations of pepsin and chloride were included.

F. F., aged 49 years, a foreman of a railroad gang, entered the Cincinnati General Hospital, in February 1931, with paralysis of the extremities following ingestion of adulterated Jamaica ginger. His past history was unimportant except for chronic alcoholism. He had been surprisingly free from digestive disturbances. The general physical examination revealed only evidence of peripheral neuritis and of some involvement of the pyramidal tracts. The blood count, urinalysis and stool analysis gave normal results. The Wassermann reaction of the blood was negative. Roentgenograms of the gastrointestinal tract were normal. The basal metabolic rate was —16 per cent.

Soon after admission to the hospital the patient regained the full use of his upper extremities. His lower extremities, however, remained permanently damaged, so that he was unable to walk, but he was able to get about readily in a wheel-chair. He was intelligent and cooperative. He was weighed twice weekly, and his blood was examined once a month.

REPEATED INJECTIONS OF HISTAMINE

Method Used.—At 9 a. m., after a twelve hour fast, a Rehfuss tube was swallowed, and the gastric contents were removed and examined. One-half milligram of histamine phosphate was given subcutaneously, and the injection was repeated one-half hour later. Continuous aspiration with a 50 cc. syringe was practiced by the patient for two and one-half hours. The total quantities

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obtained during half-hour periods were examined separately.[1] An emesis basin was always at hand to receive any saliva that might be secreted during the aspiration, but fortunately the quantity was insignificant. Frequent control observations were made under fasting conditions for two and one-half hour periods without the injection of histamine. There was generally secreted about 250 to 350 cc. of gastric juice under such conditions, in contrast with an average of 350 to 500 cc. after an injection of histamine. Attention was always paid to the presence of bile and mucus. Fortunately bile was rarely present, and the quantity of mucus was generally negligible. The juice obtained was thin, clear and colorless. The titratable acidity was determined by the standard method, Töpfer's reagent and phenolphthalein being used as indicators and titration being carried out with tenth-normal sodium hydroxide. The chloride content was estimated by the method of Van Slyke and Sendroy. The pepsin content was measured by the Mett's tube method.

Results.—Up to May 1, 1936, the patient had had 433 aspirations, carried out as outlined, and had received 799 injections of 0.5 mg. of histamine.[2] He still experienced the same effects noticed after the initial injections. There was a general tingling sensation accompanied with a feeling of warmth, which started about two minutes after the injection and lasted about four to six minutes. This was accompanied with a slight throbbing in the head and followed by slight transient headache. There was general flushing of the skin, and exceptionally an urticarial wheal developed at the site of injection. There was a slight increase in pulse rate, with no change in the arterial blood pressure.

The patient apparently incurred no harm from the injections. By May 1936 he was 30 pounds (13.6 Kg.) heavier than he was on admission to the hospital. Monthly blood counts remained within normal limits. Repeated determinations of the chloride content of the blood gave normal results. Repeated roentgenographic examinations of the gastrointestinal tract revealed normal rugae and no change in motor function. Five gastroscopic examinations were made: 4 by Dr. Samuel Iglauer with the rigid tube and 1 by Dr. Rudolph Schindler with the flexible gastroscope. The findings were not noteworthy except for those of mild superficial gastritis.

TRANSIENT ACHLORHYDRIA

A. Initial Phase (Absolute Achlorhydria).—In the first few months of study the average total volumes obtained during two and a half hour periods following the injection of histamine ranged between 170 cc. (December 1931, 8 determinations) and 250 cc. (March 1932, 8

1. On some occasions either 1 or 2 injections of histamine were given, and the gastric juice was collected during ten minute periods.

2. Between January 1935 and January 1936, 104 injections were given without subsequent aspirations.

determinations). Later these increased to between 435 cc. (December 1932, 17 determinations) and 568 cc. (December 1933, 10 determinations). In February 1934 the average volume after the injection of histamine had decreased to 332 cc. (5 determinations); in April 1934 the average volume was 365 cc. (6 determinations). The range of acidity during a corresponding period is given in chart 1.

Aspirations were not performed between May 1 and July 23, 1934; during this period no histamine was given, as studies were being made of the patient's duodenal contents. By July 24 there had developed a histamine-refractory achlorhydria associated with a disappearance of pepsin and a decrease in volume of gastric juice to 123 cc. Achlorhydria was also present on July 28 (volume, 131 cc.), August 15 (volume, 110 cc.) and September 14 (volume, 178 cc.), as shown in chart 2.

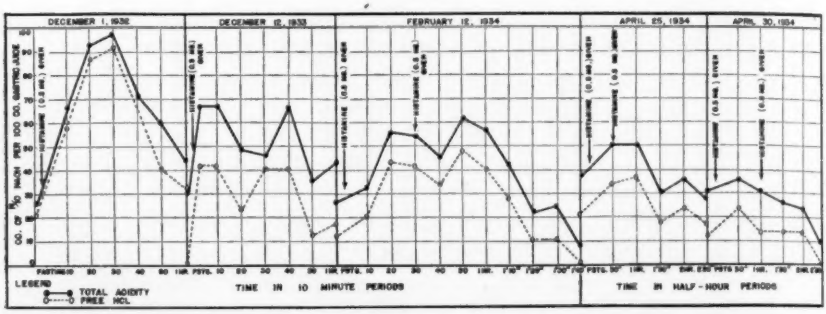

Chart 1.—Curves showing the acidity after the injection of histamine (patient F. F.).

None of the usual causes of achlorhydria, such as infection, dietary deficiency, mental or emotional strain or a bout of alcoholism, could be held accountable.

As the patient had received a total of 379 injections of histamine, the question arose as to whether or not the achlorhydria was an exhaustion effect produced by histamine. On October 12, after an injection of histamine, the gastric juice showed a return of free acidity (maximum, 14) and on November 9 a maximum acidity of 15. From January to June 1935, inclusive, the patient was given 221 injections of histamine, in the face of which there was a gradual rise in the gastric acidity, which reached normal limits in July (chart 3). From July 1935 to January 1936, inclusive, a total of 167 injections were given, the acidity remaining normal. The gradual increase in acidity and the persistence of normal values in spite of repeated injections of histamine (total, 388) would exclude an exhaustion effect.

B. Second Phase (Relative Achlorhydria).—In connection with a study of the influence of the endocrine glands on gastric secretion, the patient was given subcutaneously a total of 60,000 rat units of estrogenic substance [3] between Dec. 16 and 21, 1935, and an additional 120,000 units between Jan. 1 and 12, 1936, inclusive, in doses of 10,000 units daily, receiving in all a total of 180,000 units. During this period gastric analyses were made almost daily both with and without the injection of histamine. On January 31 the volume of gastric juice after an injection of histamine was 425 cc., and the acidity was normal. On February 3 achlorhydria was encountered in all but the second half-

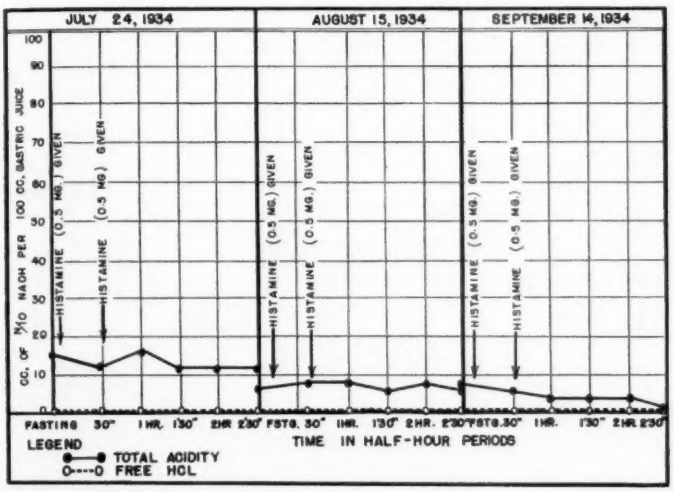

Chart 2.—Curves showing the acidity after the injection of histamine (first phase of achlorhydria, patient F. F.).

hour specimen, which showed a free acidity of only 7 (chart 4). The total volume of juice secreted during the two and one-half hour period was 375 cc., showing little decrease in contrast with the first phase of achlorhydria, in which the volume fell decidedly and in which, of course, the achlorhydria was absolute. There was no recognizable increase in the mucus content of the juice. On February 4 and 5 free hydrochloric acid was again present only in the second half-hour period after the injection of histamine, with values of 3 and 12, respectively. Daily aspiration conducted without the use of histamine between February 6 and 16 and between February 25 and March 2,

3. The preparation used was theelin.

inclusive, revealed achlorhydria in all specimens, with an average total volume of 292 cc. On February 17 and 24 the second half-hour specimen after an injection of histamine contained a free acidity of 19 and 16, respectively, the remaining specimens containing no free acid. On March 5 the specimen obtained during fasting contained a trace of

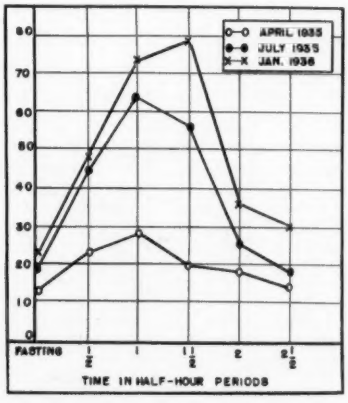

Chart 3.—Curves showing the average acidity after the administration of histamine.

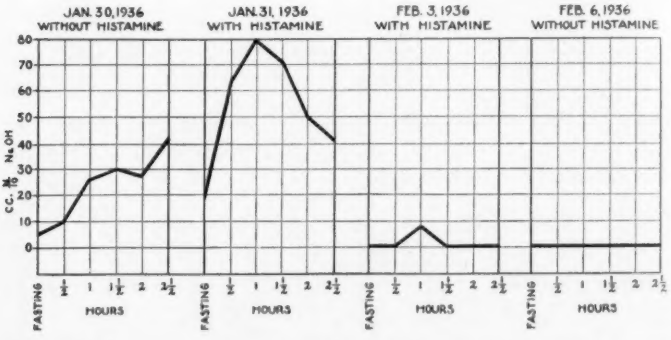

Chart 4.—Curves showing the change from normal secretion to relative achlorhydria.

free hydrochloric acid, and the fourth half-hour specimen, obtained without the use of histamine, showed a free acidity of 3. On March 11, after an injection of histamine, free acid was present in all but the fifth half-hour specimen, with a maximum value of 22. From then until May 1, 15 aspirations done without the injection of histamine showed

achlorhydria in 3 and free acid in almost all fractions in the remaining 12 specimens; while those done after the injection of histamine showed the presence of free hydrochloric acid in at least 4 specimens on 5 of 6 occasions. There was thus a gradual increase in the secretion of hydrochloric acid (chart 5).[4]

The relative achlorhydria was accompanied with an almost complete disappearance of pepsin. Again, none of the recognized causes of achlorhydria could be discovered. The estrogenic substance was suspected, and accordingly injections of it were given to three (male) patients, with no appreciable effect on gastric acidity.[5]

During each period of depressed secretion of acid the patient complained of epigastric distress immediately after meals, accompanied

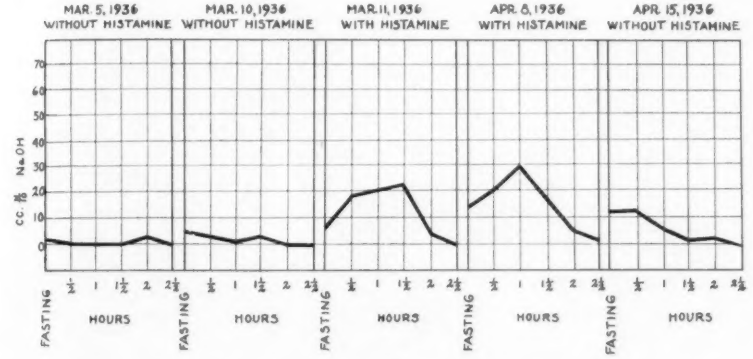

Chart 5.—Curves showing the gradual increase in free hydrochloric acid.

with considerable belching. In addition, there developed diarrhea, with an average of four to five loose, watery movements per day. Fatigability and lack of ambition were prominent. The administration of 30 drops of hydrochloric acid in a glass of water with meals was followed by partial relief.

Interestingly, gastroscopic examination revealed no gross change in the appearance of the gastric mucosa with the onset of achlorhydria. Mild superficial gastritis was encountered, a finding which had been noted four times previously.

During the second achlorhydric phase it was decided to determine whether or not the so-called intrinsic antianemic factor was still present, as it had been previously found to be. Accordingly Castle's original

4. Normal values were eventually reached.

5. Injections of estrogenic substance were given our subject in May 1937 without effect.

experiment was repeated, and two (controlled) patients with pernicious anemia were given 200 Gm. of beef muscle incubated with 250 cc. of gastric juice daily for ten days. The juice was obtained without histamine and was devoid of free hydrochloric acid. It was kept on ice until ready for use. In both instances there developed reticulocytosis, followed by an increase in the hemoglobin and red blood cell values and accompanied with marked clinical improvement, proving that the antianemic substance had not disappeared.

SUMMARY AND CONCLUSIONS

Repeated (799) subcutaneous injections of histamine phosphate in 0.5 mg. doses were given to a patient over a period of four and one-half years, with no apparent harm and without overfatigue of the mechanism of hydrochloric acid secretion.

The human stomach may temporarily lose its ability or may exhibit a marked decrease in its ability to secrete free hydrochloric acid for no definitely known reason and with no change in the mucous membrane detectable on gastroscopic examination.

Absence of pepsin may be associated with the temporary disappearance of free hydrochloric acid.

The so-called intrinsic antianemic substance may still be present during a period of (relative) achlorhydria.

CALCIFIC AORTIC STENOSIS

A CLINICAL AND ELECTROCARDIOGRAPHIC STUDY

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PATHOLOGIC PICTURE

After Mönckeberg's first description of the pathologic picture of calcific aortic stenosis, in 1904, this lesion for years was reported only rarely and was recognized only at postmortem examination. In recent years, however, clinical and roentgenologic studies have allowed its recognition during life without difficulty.

Various authors (Mönckeberg, Ribbert, Margolis, Ziellessen and Barnes, Giese, Martens and others) have investigated the underlying pathologic condition, and their findings will be reviewed here as they are necessary for a better understanding of the clinical and roentgenographic aspects.

The involvement affects the aortic ring, primarily at the roots of the valves. In the first stage of the disease only the outer layer at the site of the sinus of Valsalva is affected. Calcification then extends into the leaflets or into one of the commissures, bulges into the sinuses of the valves or forms radiating or circular buckles within the valves themselves. Deposits of lime salt may fill up the sinuses completely. From there the condition may progress into the ventricles, producing spurlike formations under the endocardium. Such formations usually extend from the posterior aortic valve as far as the large leaflet of the mitral valve. An extension from these valves to the pars membranacea septi or to the muscular portions of the septum is less frequent. Calcification of the aortic valves may occur in combination with calcification of the annulus fibrosus or may be entirely isolated. The valves themselves are thickened, have an irregular surface and are fused at the commissures. The places of fusion may shrink considerably and in so doing usually cause stenosis of the valves.

From the First Medical Division, Bellevue Hospital (Columbia University), Dr. I. O. Woodruff, director, and the Department of Laboratories, Dr. D. Symmers, director.

According to Libman, the presence and the amount of arteriosclerosis and calcification in the aorta depend on whether or not the lesions in the valves precede the involvement of the aorta by any considerable period. If stenosis occurs before lesions of any consequence have developed in the wall of the aorta, the latter may be thin and smooth.

ETIOLOGY

The etiology of calcific aortic stenosis is still unknown. In only 20 per cent of the seventy-seven cases reported was there a definite history of rheumatic fever. The solitary occurrence of the lesion, i. e., the absence of involvement of the mitral valve, the lack of appreciable thickening or shortening of the chordae tendineae, the massive deposit of calcium, the predominant occurrence of the condition in older men and the nonpresence of recent or old Aschoff bodies in the myocardium —all speak against a rheumatic etiology. As has been indicated, the early changes in Mönckeberg's sclerosis fail to disclose a primary inflammatory basis, and there are no marked arteriosclerotic changes elsewhere. The coronary arteries may reveal some degree of sclerosis in older persons, but the degree of disease of the coronary arteries is not greater than one would expect to encounter in a group of normal persons of the same age. Furthermore, the occasional occurrence of calcific aortic stenosis among younger persons also speaks against an arteriosclerotic basis.

In this discussion we are excluding those cases of calcification encountered in the course of the so-called healed subacute bacterial endocarditis described by Libman and the not infrequent examples of calcification observed in long-standing rheumatic or syphilitic heart disease.

The degenerative and infiltrative processes speak for an individual predisposition toward their formation which may exist in certain persons. While the possibility that the lesion represents the healed stage of an inflammation still remains open, its exact etiology still remains problematic. The most likely conclusion, based on our present findings, is that the disease is primarily degenerative in nature; its occurrence and extent depend on an individual predisposition toward collagen involution and lipoid and calcium deposition.

CLINICAL SIGNS

In recent American literature Christian (1931), in a postmortem study of twenty-one cases, first emphasized the clinical entity of calcific aortic stenosis, its predominant occurrence in middle-aged and elderly subjects and its slow course, resulting in relatively late cardiac failure

and occasionally in sudden death. The important classic diagnostic physical signs are a long loud rough systolic murmur transmitted to the vessels of the neck, the systolic thrill over the aortic area, frequently best felt with the patient in the knee-chest position, the absence or diminution of the intensity of the aortic second sound, especially in the vessels of the neck, and considerable cardiac hypertrophy. The soft blowing diastolic murmur of aortic insufficiency is frequently, though not invariably, heard. Usually a softer systolic murmur is heard over the mitral area and is probably due to a relative mitral insufficiency. A faint wavy or rumbling diastolic murmur is also occasionally heard at the apex (Austin Flint murmur). In cases in which there is no associated marked aortic insufficiency or hypertension, the pulse is characteristically small and anacrotic or bisferious, and the pulse pressure is normal or diminished. Occasionally the classic physical signs of aortic stenosis may not be present, leaving only the physical signs of aortic regurgitation obvious. This picture is present in the particular group of cases in which the diagnosis is frequently overlooked.

The presence of aortic regurgitation in the absence of any signs of mitral stenosis, when syphilitic heart disease can be excluded, should suggest the possibility of calcific disease of the aortic valves. In cases in which the initial insult to the valves is slight, only indistinctive clinical manifestations are produced, and heart failure consequent to the developing stenosis and subsequent death occur late. These meager clinical manifestations, without cardiac symptoms until late in the disease, and the constant presence of aortic regurgitation are strongly suggestive of calcific aortic valvulitis.

FLUOROSCOPY AND AIMED ROENTGENOGRAPHY

The number of calcifications of the cardiac valves recognized roentgenographically in vivo has increased considerably in the last four years.

Simmonds (1908) first made a roentgenographic study of calcifications of the heart in five cases at necropsy. Klason (1921) first diagnosed calcified annulus fibrosus in vivo; Fleischner (1925) and Saul (1932) reported similar cases. Christian (1931) first emphasized the potentialities of the roentgenographic demonstration of cardiac calcifications in vivo, and his collaborator, Sosman, first reported such a case. Sosman and Wosika (1933) were able to report twenty cases of calcific aortic stenosis and nineteen cases of calcification of the mitral valve observed roentgenographically before death.

Further observations of roentgenographically diagnosed intracardiac calcifications were published by Parade and Kuehlman (1933), who

saw five patients, one with calcific aortic stenosis. Sparks and Evans (1935) reported one case of calcification of the aortic valves; Bishop and Roesler (1934), three cases, all with autopsies; Blackford (1936), one case; Cooley (1936), one case; Willius (1935), sixteen cases of calcific aortic stenosis, and Kommerell (1936), ten cases in which there were four calcified aortic valves.

The proper use of roentgenoscopy and aimed roentgenography was the contributing factor in making the recognition of calcified aortic stenosis possible when clinical symptoms were rather indefinite. With aimed roentgenography the calcified depositions are localized fluoroscopically in the best view obtainable and with a special device, the serialograph, immediately roentgenographed, with an exposure of 0.05 second (75 kilovolts and 100 milliamperes).

The calcified valves show up under fluoroscopy as small dense shadows, rapidly moving or dancing up and down. They cannot be projected outside the cardiac shadow and are not affected by deep inspiration. They move more rapidly than the pulsating left cardiac border. They are seen in the median line or a little to the right of it in the lowest third of the cardiac area. They are best observed at the right oblique angle, as the movement is most marked in this view. The observer's eyes must be well adapted, and the smallest diaphragm must be used in order to obtain sharp visualization of the fine details. Experienced observers are often able to localize these calcifications. Mitral calcifications are situated more medially and show marked rapid pulsatory motion, whereas the aortic deposits of calcium show less extensive and more dancing movement. The calcifications of the annulus fibrosus have ring forms and move relatively little.

Little difficulty is experienced in differentiating the calcified valves from other calcifications. Occasionally they may be confused with calcified thrombi. Calcified coronary arteries are recognized only in exceptional cases.

Myocardial calcifications are rare. Smaller pericardial calcifications may, if the patient is turned, be projected on the cardiac margin and thus easily differentiated from endocardial calcifications. Hilar calcifications can easily be excluded.

REPORT OF CASES

We present here fourteen cases of calcific aortic stenosis. The patients were observed at Bellevue Hospital during the last seven years, with nine autopsies. Five of the patients (cases 1 to 4 and 14) are still living and under observation. It is only for the latter group, in the last few years, that we have applied systematically the roentgenographic

procedure, with correspondingly gratifying results. Except in these five cases, the correct diagnosis was not made until after death (table).

Four of the nine patients studied at autopsy had the physical findings of aortic insufficiency and suffered cardiac pain. These same four displayed the typical electrocardiographic changes of myocardial damage associated with disease of the coronary arteries. Yet all the necropsies revealed calcific aortic stenosis, with patent coronary arteries showing minimal sclerosis. All the patients who have not yet come to autopsy have revealed the physical findings of aortic insufficiency and have suffered cardiac pain. Four of these five patients have shown electrocardiographic evidence of myocardial damage. Roentgenographic examination has revealed calcific depositions in the aortic valves of all five patients. Syphilis and bacterial endocarditis were not present in any of the fourteen cases.

From the evidence just presented, it may be seen that when the physical signs of aortic insufficiency are accompanied with the electrocardiographic findings of myocardial damage and when syphilitic disease and acute and subacute bacterial endocarditis are absent, a diagnosis of calcific aortic stenosis is indicated. Roentgenographic examination will confirm or contradict this impression.

CASE 1.—J. M., a man aged 43, had had recurrent cardiac pain radiating down the left arm and shortness of breath on exertion for ten years. He had been admitted to the hospital three times because of cardiac pain and addiction to phenobarbital. There was no history of rheumatism. He complained of precordial pain caused by effort or excitement. There was no history of congestive failure.

Physical examination revealed a fairly well developed man. The pupils were equal and reacted to light and in accommodation. There was no congestion of the veins of the neck. The lungs were resonant throughout. Examination of the heart showed that the point of maximal impulse was in the sixth intercostal space 11.5 cm. from the midsternal line. A faint systolic thrill was noted over the aortic area. The second aortic sound was absent over the aortic area and the carotid vessels. The first apical sound was loud and accentuated, with a soft short diastolic murmur over the left sternal border. The blood pressure was 124 systolic and 65 diastolic. There was a Corrigan pulse; no capillary pulse was noted. The liver and spleen were not palpable. No pretibial edema was present. The Wassermann reaction was negative. The basal metabolic rate was —3 per cent. The urine was normal.

An electrocardiogram taken on April 10, 1935, showed normal sinus rhythm, with a rate of 80 per minute. The PR interval was 0.16 second and the QRS interval 0.8 second. There was no deviation of the electrical axis.

The electrocardiogram showed that QRS_1 was split and of low amplitude. The T wave was of the inverted seagull type in lead I and was inverted in all leads. The form of the T wave and its low amplitude suggested myocardial damage. At present the patient shows practically the same electrocardiographic picture as when admitted to the hospital. The initial and final ventricular complexes are characteristic of myocardial changes associated with recent closure of the coronary vessels.

Case	Sex	Age	Rough Loud Aortic Systolic Murmur	Aortic Systolic Thrill	Soft Blowing Diastolic Murmur of Aortic Insufficiency	Absent or Diminished Aortic Second Sound	Marked Cardiac Hypertrophy	Small Soft Anacrotic Pulse	Roentgen Findings	Electrocardiographic Findings	Slow Development of Congestive Failure	Dyspnea and Edema	Cardiac Pain
1	M	43	+	+	+	+	+	+	+	Inverted seagull T_1; coveplane T_2 and T_3	—	+	+
2	M	37	+	+	+	+	+	+	+	Normal sinus rhythm; no deviation; upright T wave in all leads	—	—	+
3	M	70	+	+	—	+	+	—	+	Left bundle branch block; inverted T_1; upright T_3, opposite main deflection	+	—	—
4	M	60	+	+	+	+	+	+	+	Left bundle branch block; QRS notched and slurred in all leads	+	—	—
5	M	50	+	+	+	+	+	+	—	Inverted T_1 and T_2; slurred QRS; later inverted T_1; diphasic T_2 and T_3	+	+	—
6	M	63	+	+	+	+	+	+	—	Inverted T_1 and T_2	+	+	—
7	M	39	+	+	—	+	—	—	—	Diphasic T_1, T_2 and T_3; intraventricular block	—	+	—
8	M	49	+	—	+	—	+	+	—	Inverted T_1 and T_2; diphasic T_3	+	+	—
9	M	54	+	+	+	+	+	+	—	.....	+	+	+
10	M	47	+	..	+	..	+	—	—	.....	+	—	+
11	M	68	+	..	+	—	—	—	—	.....	—	—	—
12	F	74	+	..	+	—	—	—	—	.....	—	—	—
13	M	60	+	..	+	—	—	—	—	.....	—	—	—
14	M	68	+	..	+	+	+	+	+	Normal sinus rhythm; left axis deviation	+	+	—

Syncope	Death Due to Cardiac Failure	Sudden Death	Antemortem Diagnosis	Arteriosclerotic Aortic Insufficiency	Mitral Stenosis	Necropsy Observations	Comment
—	—	—	Arteriosclerotic heart disease	+	—	.....	.....
—	—	—	Arteriosclerotic heart disease	+	—	.....	.....
—	—	—	Arteriosclerotic heart disease	+	—	.....	.....
—	—	—	Arteriosclerotic heart disease	+	—	.....	.....
—	+	—	Arteriosclerotic heart disease	+	—	Chronic aortic calcific valvulitis; aortic cusps fused, thickened, stiffened and distorted by calcareous deposits	Coronary arteries entirely free from sclerosis; diagnosis: acute coronary thrombosis with left pleural effusion
—	+	—	Arteriosclerotic heart disease	+	—	Aortic valves totally calcified; calcification covered by intima for most part, but eroded in some areas, displaying thrombi of recent origin; calcification extended on aortic surface along commissures	Coronary arteries patent throughout; showed minimal sclerosis
+	—	+	Arteriosclerotic heart disease	—	—	Calcified aortic valvulitis superimposed on congenital bicuspid aortic valve	Coronary arteries well preserved and patent
—	+	—	Arteriosclerotic heart disease	+	—	Aortic valves showed extensive deposits of calcareous granules	Orifices of coronary arteries shut off to large extent by atheromatous process
—	+	—	Calcified aortic valvulitis	+	—	Aortic cusps calcified	Coronary arteries well preserved
—	+	—	Rheumatic heart disease; mitral stenosis; aortic stenosis	—	+	Mitral valve thickened and cusps fused; aortic valves replaced by calcareous deposits which narrowed the orifices to 4 mm.; soft vegetations superimposed on calcified areas	Coronary arteries patent throughout
+	—	+	Arteriosclerotic heart disease	—	—	Atherosclerosis with calcification of mitral and aortic valves	Carcinoma of esophagus with metastasis in liver
—	—	—	Arteriosclerotic heart disease	—	—	Aortic valves thickened; calcareous ring at base of valves	Coronary arteries entirely free from sclerosis; fracture of neck of femur
—	—	—	Arteriosclerotic heart disease	—	—	Aortic cusps showed small sclerotic and calcified plaques	Coronary arteries sclerotic; lumens patent; abscess of lung
—	—	—	Arteriosclerotic heart disease; essential hypertension	+	—	.....	.....

Roentgen examination revealed a normal pulmonary parenchyma (fig. 1). The heart was slightly enlarged. The aorta was well within normal limits. Roentgenoscopy revealed rapidly pulsating calcifications of the aortic cusps.

The history of precordial pain radiating down the left arm, coming on after exertion and occasionally during rest, and dyspnea on effort, with electrocardiographic findings of a cove plane T wave in leads I to III for a young subject, strongly suggested myocardial infarction due to coronary closure, yet the roentgen evidence proved that this was a case of calcific aortic disease.

Case 2.—J. S., a man aged 37, had had precordial pain since 1922, with occasional pain down the left arm coming on after exertion and also while at rest and dyspnea on effort. He slept on two pillows and always felt tired. There was no rheumatic history. An extragenital chancre developed in November 1936.

Physical examination revealed a fairly well nourished man. The pupils were equal and reacted to light and in accommodation. There was no congestion of the veins of the neck. The heart was enlarged to the left. The point of maximal impulse was in the sixth intercostal space 11 cm. from the midsternal line. A

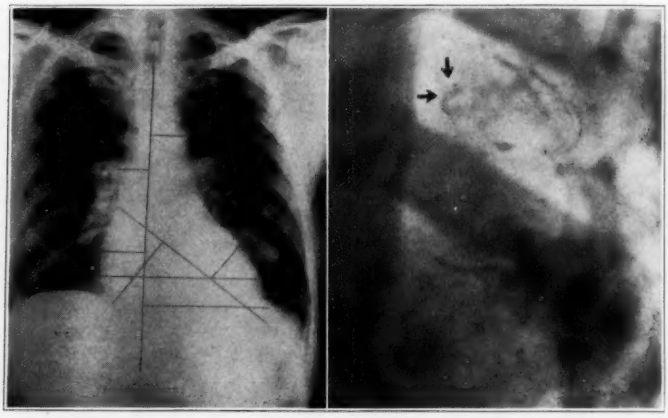

Fig. 1.—Roentgenographic appearance in case 1.

systolic thrill was noted over the aortic area. The aortic second sound was absent over the carotid and aortic areas. A loud rough systolic murmur was noted over the aortic area and over the left sternal border. There was a short apical systolic murmur, with a mid-diastolic murmur over the apex (Austin Flint murmur). There was a normal sinus rhythm. The blood pressure was 102 systolic and 70 diastolic. The liver and spleen were not felt. There was no pretibial edema.

The electrocardiogram showed a normal sinus rhythm. There was no deviation of the electrical axis. The T wave was upright in all leads.

Roentgen examination revealed mitral configuration of the heart, within normal limits, and hypertrophy of the left ventricle. The aorta was moderately elongated and widened, with characteristic dancing calcific depositions in the aortic cusps (fig. 2).

Case 3.—R. H., a man aged 76, had had symptoms of cardiac pain on exertion since 1934. There were no attacks suggesting coronary occlusion. The patient's

chief complaints were of dyspnea on exertion, dizziness and general weakness. There was no history of paroxysmal nocturnal dyspnea or congestive failure.

Physical examination revealed a well preserved asthenic man. Arcus senilis and kyphosis of the dorsal portion of the spine were noted. There was no congestion of the veins of the neck. The chest was clear. The heart was moderately enlarged. The apex beat was in the fifth intercostal space 12 cm. from the midsternal line. There was no precordial thrill. An aortic second sound was faint over the aortic area. A loud rough systolic murmur was heard over the aortic area. There was a normal sinus rhythm. The blood pressure was 190 systolic and 100 diastolic. The radial and carotid arteries were thickened and tortuous. There was no pretibial edema.

An electrocardiogram showed a normal sinus rhythm. There was left axis deviation. The QRS interval was 0.14 second and the PR interval 0.18 second. The

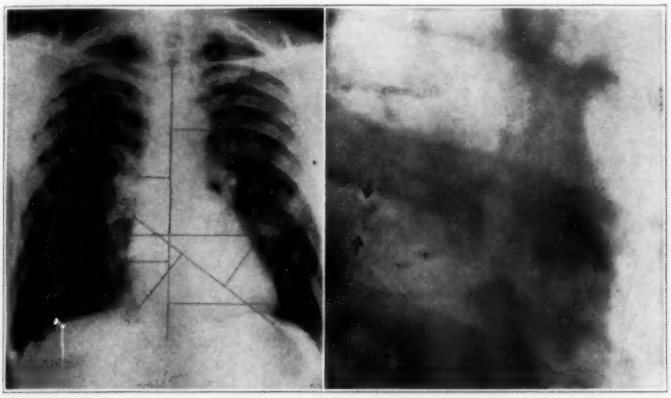

Fig. 2.—Roentgenographic appearance in case 2.

QRS complex was notched and slurred in all leads. T_1 was inverted and opposite to the QRS deflection. There was left bundle branch block.

Roentgen examination of the heart revealed an aortic and tricuspid configuration, marked enlargement, moderate widening of the aorta, with dancing aortic calcifications, and pulmonary fibrosis (fig. 3).

CASE 4.—J. C., aged 60, a seaman, first noticed symptoms of heart disease in 1925. On admission to the hospital he complained of dyspnea, palpitation and dizziness. There was no history of edema of the ankles or precordial pain. In 1934 he contracted a heavy cold, with a hacking cough, and since then had had increased dyspnea and had found it necessary to sleep on two pillows. During the past two years he had had three syncopal spells.

Physical examination revealed an emphysematous chest. The heart was slightly enlarged. The apex beat was noted in the fifth intercostal space 11 cm. from the midsternal line. A systolic thrill was noted over the aortic area. The blood pressure was 120 systolic and 80 diastolic. There was a normal sinus rhythm, with occasional premature beats. An aortic second sound was not heard over the aortic area or over the vessels of the neck. There was a rough loud systolic

apical murmur, with a soft diastolic murmur over the aortic area. There was marked sclerosis of the radial and carotid arteries.

An electrocardiogram revealed a normal sinus rhythm and left bundle branch block. The PR interval was 0.18 second and the QRS complex 0.15 second. There

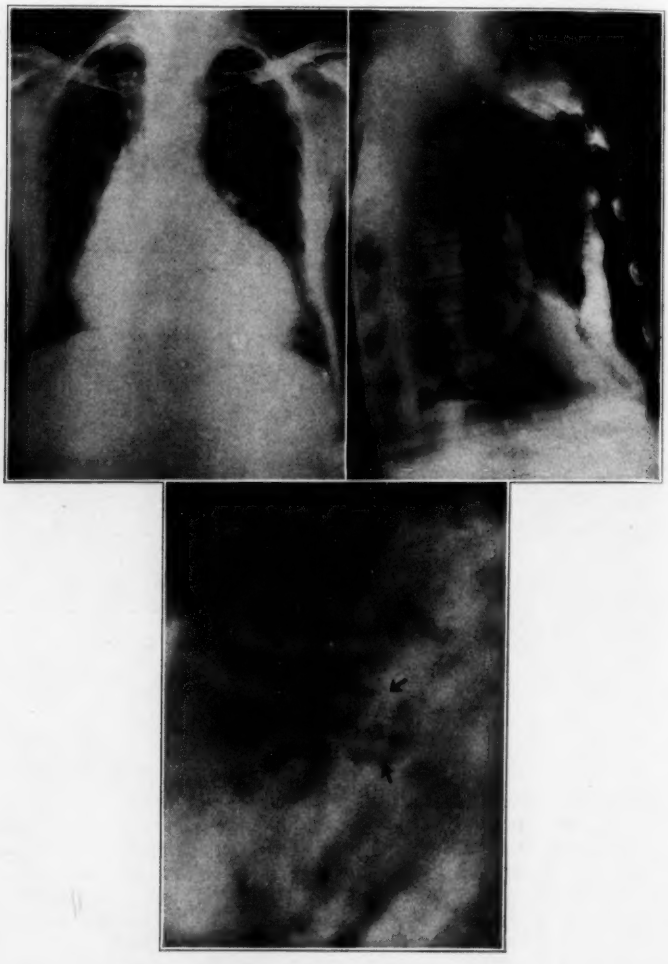

Fig. 3.—Roentgenographic appearance in case 3.

was left axis deviation. The QRS complex in all leads was notched and slurred. The ST segment was concave in lead I. T_3 and T_2 were upright. The T wave was opposite to the main deflection in leads I and III.

Roentgen examination demonstrated a hypertensive heart, with moderate enlargement. The aorta was moderately elongated and widened and of increased density and pulsation, with dense pulsating calcifications in the area of the aortic cusps. Pleural calcifications were present (fig. 4). There was marked calcification of the tibial arteries.

CASE 14.—J. P., a man aged 68, was first seen in 1931. He had a history of epistaxis and shortness of breath for the past three months, which cleared up slowly with rest in bed and digitalis. There was no history of cardiac pain. The patient was readmitted to the hospital on Feb. 2, 1935, with mild congestive failure and pretibial edema. Since then he has had exertional dyspnea. There was no history of rheumatic fever.

Physical examination revealed a well developed asthenic man. The pupils reacted equally to light and in accommodation. Examination of the fundus showed marked retinal sclerosis. There was no congestion of the veins of the neck. The

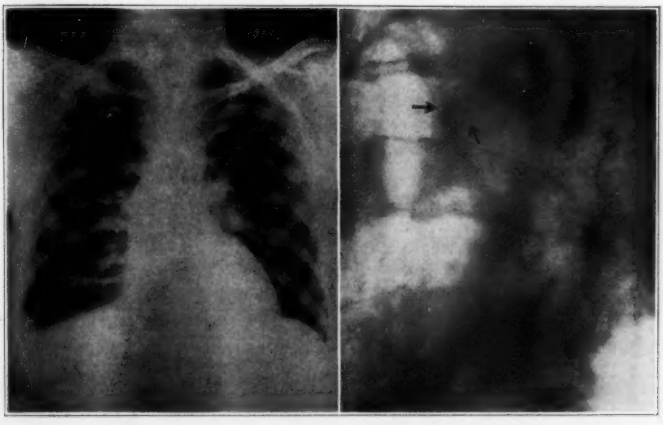

Fig. 4.—Roentgenographic appearance in case 4.

lungs were resonant throughout. Examination of the heart showed that the point of maximal impulse was in the sixth intercostal space 12 cm. from the midsternal line. There was a systolic thrill over the aortic area. An aortic second sound was faint but present over the vessels of the neck. There was a harsh loud systolic murmur over the mitral area. The sinus rhythm was normal. The blood pressure was 170 systolic and 90 diastolic. There was a small Corrigan pulse. Marked sclerosis of the radial arteries was noted.

The Wassermann reaction was negative. Urinalysis showed faint traces of albumin, with occasional hyaline casts.

Electrocardiograms were taken in 1931 and on March 13, 1937, and revealed a normal sinus rhythm, left axis deviation and no evidence of myocardial damage.

Roentgen examination revealed a normal pulmonary parenchyma (fig. 6), moderate hypertrophy of the heart, accentuation of the left ventricular curve and slight dilatation and tortuosity of the aorta. Roentgenoscopy revealed a single sharply outlined density the size of a pea in the area of the aortic cusps, showing slow vertical oscillations independent of the respiratory excursions.

EXPLANATION OF FIGURE 5

Fig. 5.—*A*, case 1. Tracing made on April 10, 1935. Note the inversion of T in all leads. *B*, case 1, Dec. 10, 1936. *C*, case 1, March 5, 1937. Note that T is flat and markedly inverted in leads II and III. *D*, case 4, April 2, 1934. Note the intraventricular block. *E*, case 4, April 30. *F*, case 4, March 7, 1937. Note the left bundle branch block. *G*, case 3, Oct. 23, 1934. *H*, case 3, Feb. 5, 1937. Note the left bundle branch block. *I*, case 5, Feb. 13, 1935. Note the inverted T_1, the diphasic T_2 and T_3 and the convex RT segment. *J*, case 5, May 20. Note the inverted T_1 and T_2, the split QRS_3 and the diphasic T_3. *K*, case 6, March 27, 1933. Note the inverted T_1 and T_2. *L*, case 7, Oct. 23, 1936. Note the intraventricular block, the diphasic T_1 and T_3, the notched and slurred QRS and the deflections in all leads.

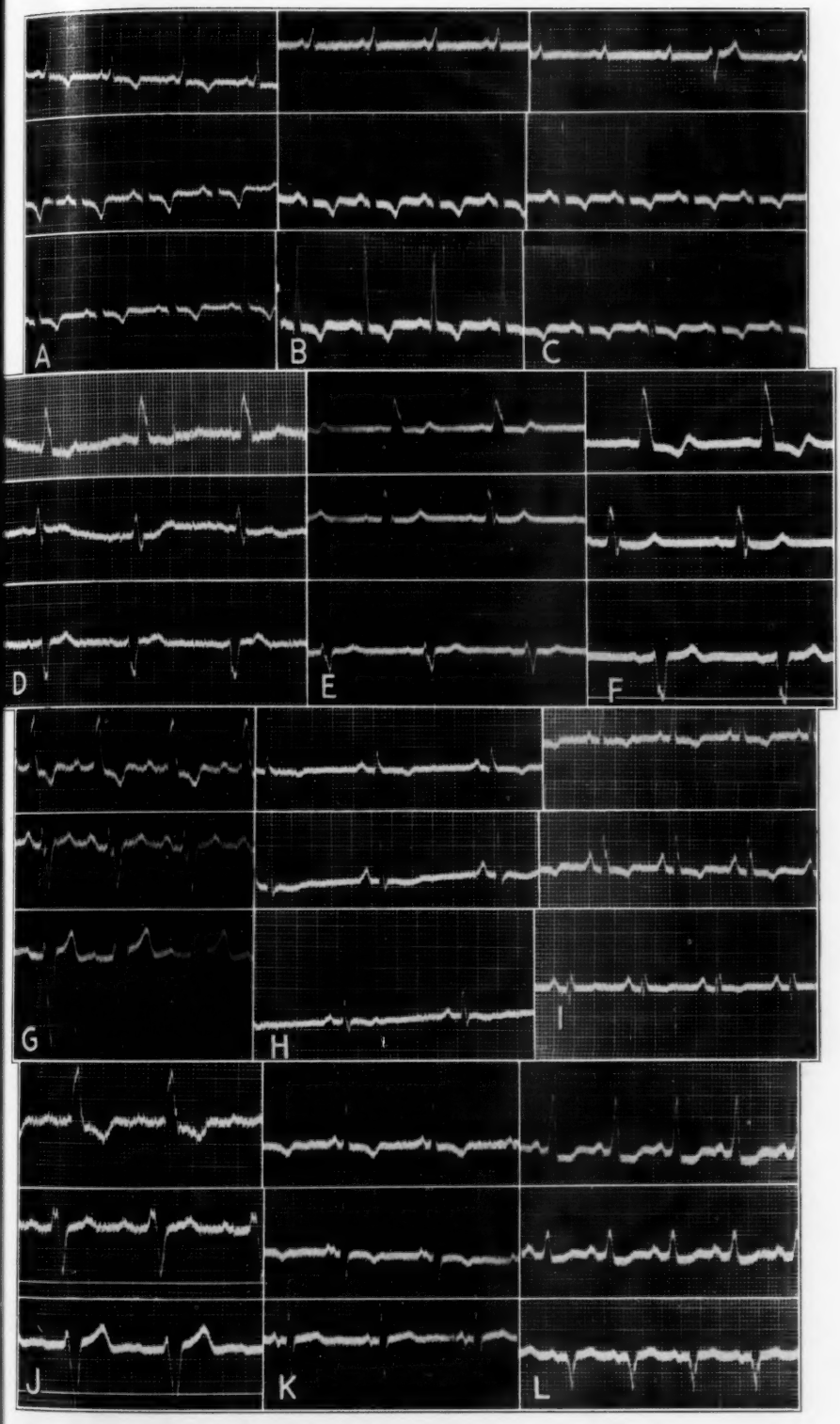

Figure 5

ELECTROCARDIOGRAPHIC CHANGES

The great majority of the changes in the electrocardiogram produced by calcific aortic valvulitis do not differ in any specific manner from some of those produced by myocardial disease due to coronary closure or by hypertrophy of the left ventricle. Electrocardiographic changes of the type most frequently seen with calcific aortic valvulitis consist of a modification of both the initial and the final deflection of the ventricular complex. The alterations which were noted are presented in detail.

T Wave.—In case 1 there was an inverted T_1, cove plane in T_2 and T_3, characteristic of myocardial damage associated with disease of the coronary arteries. In this case the initial deflection (R summit) became

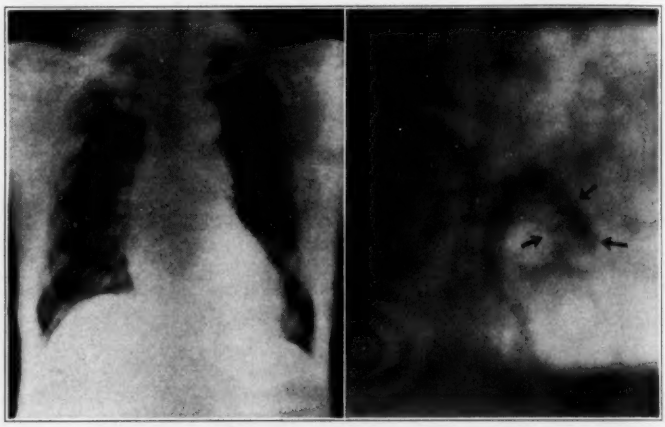

Fig. 6.—Roentgenographic appearance in case 14.

smaller. In case 4, T_2 was diphasic and T_3 inverted, later changing so as to be typical of left bundle branch block, with T_1 inverted and T_3 upright (fig. 5). There were the same electrocardiographic findings as noted in case 3. T_1 and T_2 were inverted in cases 5 and 6. Marked inversion of T_1 and T_2 and a diphasic T_3 were seen in cases 7 and 8. An upright T wave was seen in cases 2 and 14.

QT Interval.—The QT interval has been used as a measure of electrical ventricular systole. This interval was found prolonged in cases of left bundle branch block, as seen in cases 3, 4 and 7.

PR Interval.—The P wave was normal in all cases except case 3, in which there was a prolongation of the PR interval to 0.2 second.

QRS Complex.—The QRS complex was normal in all but three cases (3, 4 and 7), in which characteristic findings of left bundle

branch block and intraventricular block were found. A depressed ST segment was found in case 7.

Arrhythmia.—A normal sinus rhythm was present in all cases except for the occurrence of a ventricular extrasystole in cases 1 and 3.

Comment.—The popular view, supported by many investigations, is that the electrocardiographic changes due to myocardial damage after coronary thrombosis are of two types: (*a*) inverted T_1 and T_2 (Q_1, T_1 type) and (*b*) inverted T_2 and T_3 (Q_3, T_3 type). There is still another type of old coronary thrombosis in which the electrocardiographic changes are not typical of these two types, and they may well be confused with the electrocardiographic changes of calcific aortic stenosis. There is sufficient similarity so that the two types might be confused if the electrocardiographic findings alone were considered. The fact that electrocardiographic changes persist over a long period without any change in the electrocardiogram is suggestive of their association with calcific aortic stenosis.

Left bundle branch block was seen in cases 3, 4 and 7 and was rather frequent (21 per cent) in our small group. With the possible exception of hypertensive heart disease, no other clinical entity produces left bundle branch block in such a high percentage of cases. The most likely explanation of left bundle branch block produced by calcific aortic valvulitis is that it is due to the involvement of the conduction system by large calcific projections of the aortic valve.

Although electrocardiographic changes produced by calcific aortic valvulitis are not characteristic of the classic type of acute coronary thrombosis, the findings are those usually considered to be characteristic of severe myocardial damage, with the inversion and coving of the T wave frequently seen with conditions causing hypertrophy of the left ventricle and with coronary thrombosis.

COMMENT

With the growing understanding of the clinical picture of calcific aortic valvulitis, it is increasingly evident that not infrequently the only clinical signs and manifestations are those of aortic regurgitation, and therefore an erroneous diagnosis is often made.

Although the most common etiologic factor in uncomplicated aortic valvulitis is syphilitic infection which produces a specific type of arteriosclerosis of the aorta and analogous scarring and retraction of the aortic valves, with separation of the commissures, this specific lesion practically never produces deposition of calcium in the valves such as is seen in calcific aortic stenosis.

In other words, pure aortic insufficiency, not due to syphilitic disease or to acute or subacute bacterial invasion of the valve, may be

due to calcific aortic valvulitis. This is especially true of the group of conditions which were formerly thought to be due to arteriosclerosis in which the signs of aortic stenosis were indefinite.

Frequently, aortic regurgitation is observed in middle aged or elderly adults, with or without hypertension, who show a negative Wassermann reaction, and is incorrectly diagnosed as sclerotic aortic regurgitation. A careful review of necropsy reports at Bellevue Hospital in cases of this type failed to confirm the clinical findings of arteriosclerotic aortic regurgitation. In all these cases necropsy revealed calcific aortic stenosis.

This new point of view throws further light on the early stage of the disease. Several of our patients have been followed for four or five years, with few clinical symptoms. Only in later life are there positive signs of aortic stenosis. Cardiac pain, heart failure and syncope occur late in the life cycle in this disease.

The electrocardiographic changes in many of our cases of calcific aortic stenosis are the same as those seen with myocardial damage associated with hypertrophy of the left ventricle and disease of the coronary arteries. This may be explained on the basis of interference with the coronary blood flow due to the large calcific projections of the aortic valve into the sinus of Valsalva, because the orifices and the lumens of the coronary arteries are well preserved and patent, as seen at necropsy in the majority of our cases. Another explanation is that the myocardium is suffering from anoxemia due to the hydrodynamic changes resulting from jet formation.

Marvin, in a review of his cases, attempted to explain the sudden death and syncope seen with aortic stenosis as due to hyperactivity of the carotid sinus reflex. We have not found in our cases any abnormality of this reflex. It would also be possible to explain syncope and cardiac death as due to morphologic changes involving the cardiac muscle and its conduction system.

The association of syncope and cardiac pain in these subjects is frequently mistaken for coronary thrombosis. The correct diagnosis of calcific aortic valvulitis is frequently made only at necropsy, especially if the physical signs of aortic stenosis are indefinite.

If it is borne in mind that electrocardiographic tracings with these two conditions may be similar, the use of roentgenoscopy and aimed roentgenography may help to detect the calcific depositions and lead to a correct diagnosis.

SUMMARY

Fourteen cases of calcific aortic stenosis are reported, with clinical and electrocardiographic findings and nine autopsy examinations. Roentgen diagnosis was made in the remaining five cases.

Today careful clinical and roentgenographic examination make it possible to diagnose calcific aortic stenosis in vivo as a routine procedure. In our series a clinical diagnosis of arteriosclerotic aortic regurgitation or myocardial infarction was invariably made.

In a certain group of cases of calcific aortic stenosis the only clinical manifestations are those of aortic regurgitation.

In some of our cases electrocardiographic changes were presented which did not differ in any specific manner from those due to myocardial changes associated with disease of the coronary arteries. The presence of cardiac pain and syncope in these cases may lead to the erroneous diagnosis of coronary thrombosis.

We wish to emphasize, therefore, that in cases of aortic regurgitation in which there are electrocardiographic findings of myocardial damage and no evidence of syphilitic or rheumatic heart disease, a proper roentgenoscopic and roentgenographic examination may reveal characteristic depositions in the aortic valves.

OSSEOUS FORM OF GAUCHER'S DISEASE

REPORT OF A CASE

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An excellent review of the osseous form of Gaucher's disease may be found in the article by Ludwig Pick.[1] We are reporting this case of Gaucher's disease because of the extensive osseous changes and the unusual hematologic findings.

REPORT OF CASE

Sidney F., a Polish Jew, 26 years of age, was admitted for the last time to the Montefiore Hospital on Nov. 28, 1934. His parents and four brothers and sisters were living and well.

History.—In 1921 he was incapacitated by intermittent pain, swelling and at times redness, commencing in the knee joints and soon involving the hips, shoulders, elbows and ankles. There was no fever. The arthritic pains were believed to be rheumatic. In 1922 a diagnostic puncture of the enlarged spleen showed the patient to be suffering from Gaucher's disease. During the next four years the articular pains recurred frequently and with increasing severity. Progressive enlargement of the spleen and marked pallor were noted. In 1926 severe nasal and oral hemorrhages occurred. There was marked enlargement of the abdomen and at times urinary incontinence. In 1928, because of the hemorrhagic phenomena, consequent anemia and symptoms of pressure from the greatly enlarged spleen, this organ was removed. After splenectomy the hemorrhages ceased, the anemia disappeared and the patient experienced relief from the articular pains and gained weight. From 1928 to 1930 he was frequently hospitalized because of recurring pains in the joints. In 1930 he was again hospitalized because of pain in the back. At this time a gibbus was noted in the dorsal region. In 1931 hepatic enlargement appeared. In 1932 walking was difficult even with the aid of a back brace. In 1933 a fracture of the sternum, with regional swelling of the soft parts, was noted. By 1934 the patient's height had decreased from 60 to 40 inches (150 to 100 cm.). For eight months he had been bedridden. A blood-tinged expectoration, associated with a rise in temperature to 102 F., interpreted as due to bronchopneumonia, had troubled him for three months. At the time of his last admission to the hospital, weakness and skeletal pains were his chief symptoms.

Examination.—Physical examination revealed a poorly nourished man. The skin was yellowish brown, dry and inelastic. Bilaterally a pinguecula was present

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From the medical service of Dr. Leopold Lichtwitz, Montefiore Hospital.

1. Pick, L.: Ergebn. d. inn. Med. u. Kinderh. **29**:519, 1926.

at the inner canthus. There was marked pallor of the conjunctival and oral mucous membranes. Numerous small discrete nontender shotty glands, ranging from the size of a pea to that of a hazelnut, were felt in the cervical, axillary and inguinal regions.

The thoracic cage was considerably deformed. Marked dorsal kyphosis extended from the sixth to the tenth dorsal vertebra. Lordosis was present in the lumbar region. The anteroposterior diameter of the chest was increased. There was flaring of the lower ribs. Tenderness to pressure was present from the sixth to the tenth dorsal vertebra. There were dulness, rales, increased tactile fremitus and increased breath and voice sounds at the base of the right lung.

Examination of the heart revealed no abnormality. The blood pressure was 104 systolic and 76 diastolic. A scar from a left rectus incision was present. The liver was smooth and slightly tender and extended into the right iliac fossa. The left lobe was felt beneath the left costal margin. There was slight clubbing of the fingers. Neurologic examination revealed no abnormality.

Laboratory Data.—On December 14 a blood count showed: hemoglobin, 48 per cent (7.2 Gm.); red blood cells, 2,900,000; nucleated cells (red and white), 23,000; white blood cells, 6,000; nucleated red blood cells, 17,000; platelets, 90,000; segmented polymorphonuclears, 20 per cent; staff cells, 20 per cent (only 50 white cells were counted); lymphocytes, 40 per cent; monocytes, 20 per cent, and reticulocytes, 6 per cent (half with and half without nuclei). The red blood cells showed marked anisocytosis and poikilocytosis. Their size was slightly below normal. Polychromasia and basophilic stippling were present. Occasional Howell-Jolly bodies were seen (fig. 1). The platelets were larger than normal and did not stain as dark as usual.

The bilirubin content of the blood was 0.3 mg. per hundred cubic centimeters, and the icterus index, 4.

Blood fragility and resistance tests showed beginning hemolysis with 0.44 per cent solution of sodium chloride (with 0.44 per cent solution for a control subject) and complete hemolysis with 0.28 per cent solution of sodium chloride (with 0.32 per cent solution for a control subject). The results of the Hamburger test are shown in figure 2. There was a marked shift to the right, indicating an increased resistance of the red blood cells. The bleeding time was two minutes; the coagulation time, one minute, and the clot retraction time, one hour. The tourniquet test gave negative results.

From the foregoing data it was concluded that there was marked hypochromic microcytic anemia, characterized by dysfunction of the bone marrow rather than an increase in the destruction of blood. There was a remarkable outpouring of immature red blood cells, as evidenced by the polychromasia; the basophilic stippling, the reticulocytes, the normoblasts and the increased resistance of the red blood cells. Slight lymphocytosis and thrombopenia were noted but no corresponding purpuric changes.

Chemical analysis of the blood showed: sugar, 80 mg.; urea nitrogen, 11.3 mg.; calcium, 10.4 mg.; phosphorus, 2.9 mg.; cholesterol, 138 mg., and cholesterol esters, 101 mg., per hundred cubic centimeters. The Wassermann reaction of the blood was negative.

According to the congo red method, the cell volume was 28 per cent and the plasma volume 72 per cent. The plasma volume was estimated at 35 cc. per kilogram of body weight and the total blood volume at 50 cc. per kilogram. The congo red test showed that 90 per cent of the dye remained in the blood stream after one hour. There was no amyloidosis.

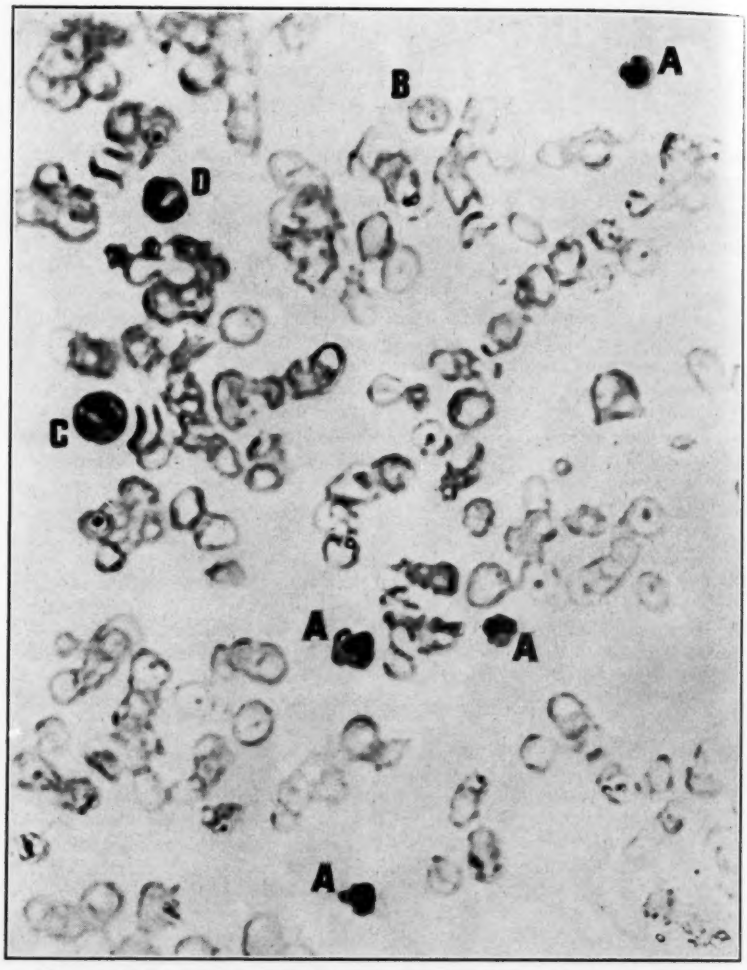

Fig. 1.—Blood smear. *A* indicates nucleated red blood cells; *B*, a red blood cell; *C*, a polymorphonuclear cell; *D*, a polymorphonuclear staff cell.

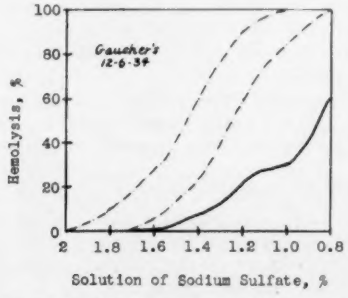

Fig. 2.—Chart showing the fragility of the red blood cells in solutions of sodium sulfate. The values along the ordinate indicate the percentage of hemolysis. The values along the abscissa indicate the percentage of the solution of sodium sulfate. The broken lines indicate the limits of the normal values. The solid line indicates the patient's curve, showing the increased resistance.

Hepatic function tests showed no bile in the urine, a marked increase of the urobilin content and a marked increase of the urobilinogen content (1:300 dilution [normal, 1:10 or 1:20]). The bromsulphalein excretion test showed that 50 per cent of the dye remained in the blood stream after a half hour. This was abnormal. All these findings indicated hepatic dysfunction.

Urinalysis showed: specific gravity, 1.013 to 1.028; albumin, + to ++, and sugar, 0. Microscopic examination revealed no abnormality.

The electrocardiogram showed left axis deviation.

The basal metabolic rate was +44 and +40 per cent, respectively, on two occasions, and the oxygen consumption was 317 and 325 liters, respectively.

Roentgen examination of the skeleton showed extensive changes. There was marked destruction of the fifth dorsal vertebra. The body of the seventh dorsal vertebra was collapsed to one third its normal size; it was somewhat elongated and extended slightly beyond the borders of the contiguous vertebral bodies. The body of the ninth dorsal vertebra showed marked absorption. The bodies of the eleventh dorsal and of the first lumbar vertebra were collapsed to about one-third their normal size. The space between the twelfth dorsal and the first lumbar vertebra was obliterated. Absorption and some narrowing of the body of the fourth lumbar vertebra was present (fig. 3).

The pelvis showed cystic changes in both innominate bones, especially in the region of the acetabulum and of the pubic bones. Small areas of osteosclerosis were also present. Hypertrophic arthritic changes were noted in the left sacro-iliac synchondrosis (fig. 4).

The femurs showed marked involvement. The head of the left femur was irregular in outline and flattened and showed areas of bone sclerosis as well as cystic areas. The shaft was broadened and showed marked cystic areas. The distal end was bottle shaped and showed areas of absorption. The right femur was similarly involved.

The left tibia showed areas of osseous absorption in the proximal and middle thirds. Slight bowing of the shaft of the left fibula was present. Areas of osseous absorption were noted in the middle third of the right tibia.

The right humerus showed areas of absorption in the head and neck and bone sclerosis in the upper third of the shaft.

Absorption of bone was noted in the lower end of the left radius.

All the ribs showed marked calcium absorption.

A pathologic fracture of the first dorsal vertebra was noted on Jan. 15, 1935.

The skull was normal.

Course.—During his stay in the hospital the patient complained of skeletal pains and marked weakness. A productive cough and pitting edema of the ankles were present. On April 16 the temperature rose to 104 F. and remained slightly elevated the next day. On April 18 he was confused, and he had spells of vomiting and expectorated blood-tinged sputum. Stiffness of the neck, stupor and a temperature of 96 F. were present on April 20, the day of death.

The hematologic data obtained during the patient's stay in the hospital are charted in the accompanying table. As can be seen, the anemia became progressively worse, the number of normoblasts fell considerably, the red blood cells changed from microcytes to macrocytes and abnormal white blood cells appeared.

Postmortem Examination.—The autopsy was performed by Dr. Henry Unger. Only the essential data are presented here.

The diagnosis was as follows: Gaucher's disease (osseous type), with involvement of the liver, lymph nodes, spinal column, pelvis, left femur, right humerus

Fig. 3.—Roentgenogram of the spine.

Fig. 4.—Roentgenogram of the pelvis.

and left radius; status postsplenectomy; heterotopic bone-marrow formation in the liver; bronchopneumonia, and bronchiolitis obliterans.

The liver weighed 4,100 Gm. and extended into the right iliac fossa. The capsule was smooth and translucent. The cut surface showed the parenchyma to be almost completely replaced by irregular confluent waxy-colored areas interspaced with yellow areas. In some places the lobular structure was still evident. The periportal regions were widened and pale yellow. A reddish area, the size of a walnut and well demarcated from the parenchyma, was present in the right lobe. Microscopically the periportal spaces showed an increase in connective tissue, in which numerous Gaucher cells were embedded. In places the nests of Gaucher

Summary of Data

Date	Hospital*	Hemoglobin, %	Erythrocytes, Million	Leukocytes, Thousand	Polymorphonuclears, %				Myelocytes, %	Myeloblasts, %	Lymphocytes, %	Monocytes, %	Reticuloeytes, %	Platelets, Thousand	Normoblasts per 100 Leukocytes	Bleeding Time, Minutes	Clotting Time, Minutes	Tourniquet Test
					Segmented	Staff	Young	Eosinophils										
8/24/25	M. S.	50	3.2	6	41	..	..	..	...	..	57	2	..	140	0	2.5	3.5	+
1/28/28	J.	55	3.4	4	36	..	..	..	...	..	60	4	5	300	0	2.0	9.0	..
								Splenectomy										
2/ 9/28	J.	52	3.8	11	74	..	4	1	4.0	..	17	..	..	350	0	1.0	2.0	..
4/ 4/28	J.	75	...	11	65	..	..	..	...	..	35	..	..	...	...	...	...	..
1/30/30	J.	66†	4.2	10	50	..	..	3	...	..	40	7	1	180	2	1.0	4.0	..
2/21/31	J.	74†	4.0	11‡	..	..	..	..	...	..	..	..	..	...	10	...	...	..
12/26/31	M. S.	79	5.1	14	47	..	..	..	...	..	49	3	2	...	8	1.5	7.0	—
								Normal										
1/10/32	M. S.	80	...	..	..	..	..	..	..	..	..	..	..	...	...	...	...	..
1/29/32	M. S.	83	5.1	18	72	12	..	..	...	..	12	4	..	...	...	...	...	..
5/13/32	J.	70	4.6	..	..	..	..	..	...	..	..	..	..	...	3	...	...	..
4/30/33	M. S.	85	4.5	10	39	5	..	..	...	..	52	4	3	260	32	...	...	..
7/17/33	M. S.	74	...	13	58	..	..	..	...	..	..	..	..	...	...	...	...	..
12/18/33	M. S.	75	...	11	67	..	..	..	...	..	30	3	..	...	213	...	...	..
12/20/33	M. S.	80	4.7	13	47	..	..	5	...	..	45	3	9	...	200	...	...	..
4/17/34	J.	61†	4.2	16‡	52	..	..	..	2.5	..	38	..	..	250	20	0.7	5.0	..
9/10/34	J.	45¶	...	..	..	..	..	..	...	..	..	..	..	...	75	...	...	..
9/15/34	J.	58	2.8	..	..	..	..	..	...	..	..	..	..	...	...	...	...	..
10/ 2/34	J.	55	4.0	..	..	..	..	..	...	..	..	..	..	90	...	...	...	..
12/14/34	M.	48¶	2.9	6‡	20	20	..	..	...	..	40	20	6	90	280	...	...	..
2/ 2/35	M.	..	...	..	18	10	5	2	8.0	2	50	5	..	...	190	...	...	..
3/ 4/35	M.	37¶	2.4	12‡	60	8	1	..	2.0	2	26	..	..	...	210	...	...	..
4/ 2/35	M.	25¶	2.1‖	9‡	52	10	3	..	1.0	4	25	5	..	...	71	...	...	..

* M. S. indicates Mount Sinai Hospital; J., Jewish Hospital; M. Montefiore Hospital.
† Dare hemoglobinometer.
‡ Corrected white blood cell count.
¶ Sahli hemoglobinometer.
‖ The erythrocytes showed definite macrocytosis.

cells compressed the hepatic cells. The circumscribed area in the right lobe proved to be heterotopic bone marrow and contained cells of the myelopoietic and erythropoietic series.

The lymph nodes (mediastinal, tracheobronchial, iliac, inguinal and mesenteric) were soft and somewhat enlarged. The cut surfaces were bright yellow. Microscopic examination showed that only a few of the follicles were preserved. The sinuses were widened and contained numerous large mononucleated and multinucleated Gaucher cells and some lymphocytes. The reticulum was filled with large clusters of Gaucher cells. The reaction for iron pigment was strongly positive.

The osseous system showed marked involvement. A sharp gibbus was noted in the upper dorsal region and a forward bulge of the sternum in the region of the manubrium sterni.

There was marked destruction of the vertebrae from the fifth dorsal to the first lumbar vertebra (fig. 5). The cut surface of the upper thoracic vertebrae was pinkish and contained small yellowish foci; the lower thoracic and lumbar vertebrae were filled with very friable granular yellowish red tissue. The cancellous tissue was readily removed, leaving only a thin cortical shell. Some of the intervertebral disks were completely separated from their contiguous vertebrae. For the most part, the disks were preserved; however, some of them were flattened and showed an absence or herniation of the nucleus pulposus. On the posterior aspect, between the third and the fourth lumbar vertebra, the disk was flat, and

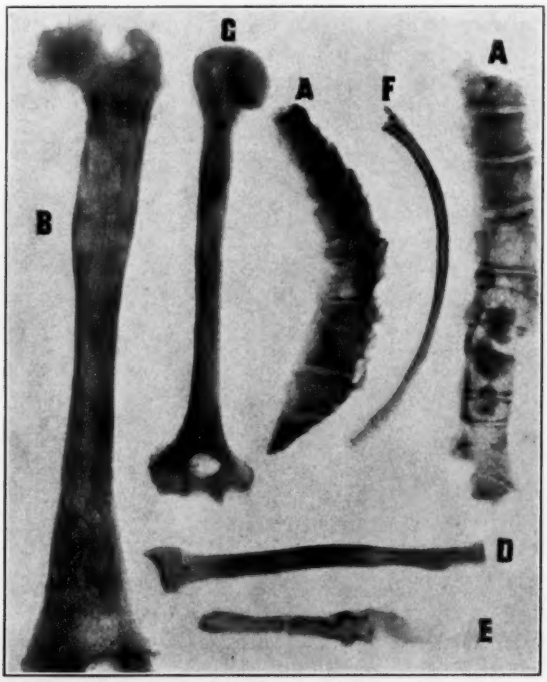

Fig. 5.—Roentgenographic appearance of the anatomic specimens: *A*, vertebral column; *B*, left femur; *C*, right humerus; *D*, right radius; *E*, sternum; *F*, rib.

the nucleus pulposus had expanded and herniated into the third lumbar vertebra. The disks between the twelfth dorsal and the first lumbar vertebra and between the first and the second lumbar vertebra were partially resorbed, the remaining portions herniating into the contiguous vertebrae, which were eburnated.

The fourth, sixth and seventh dorsal and the second and third lumbar vertebrae were examined histologically. The cortex of the fourth dorsal vertebra was, for the most part, intact. The medullary cavity showed marked resorption of the horizontal trabeculae, considerable fibrosis and round cell accumulations. The fibrous ring of the intervertebral disk was invaded by numerous blood vessels.

The sixth and seventh dorsal vertebrae, in addition to the changes previously enumerated, showed numerous Gaucher cells in the medullary cavity. The second and third lumbar vertebrae showed marked rarefaction of the trabeculae of the cortex and medulla. Large necrotic areas were present in the cortex and in the medulla. The intervertebral disk was highly vascularized. The nucleus pulposus showed partial fibrosis and was invaded by numerous mononuclear elements.

The cortex of the manubrium sterni was thinned out, and a fracture was present in the midregion (fig. 5). The cancellous bone was broken down, and the pinkish marrow was soft. The cortex of the body of the sternum showed irregular thickening.

The costochondral junction of the fifth rib was sharply demarcated. The medulla was narrow. Near the cartilage there was some softening.

The head of the right humerus contained a soft red area the size of a cherry. The rest of the head was sclerotic, and there was a marked increase of the bony trabeculae. The lumen of the proximal diaphysis was narrowed, and in places the cortex and medulla were fused. The medullary cavity of the shaft contained yellow and red-mottled friable material. The humeroscapular and elbow joints appeared normal (fig. 5).

The medullary cavity of the left radius was narrowed, and the density of the cancellous bone was increased. At the level of the tuberosity there was an area of bright yellow friable tissue the size of an almond surrounded by a thin red zone.

The head of the left femur was markedly flattened. The lower proximal portion of the articular surface was completely destroyed, and the cartilage was absent. Beneath the area of the most marked depression of the head of the femur was an area of softening, the size of a navy bean, filled with soft, elastic translucent grayish pink tissue. In the medial region of the head several nodules of friable yellowish tissue completely replaced the normal structure. The upper third of the shaft was widened, and the medullary cavity in the proximal half was filled with well delineated brownish red and yellow tissue. In the distal half, small dark red cystic areas surrounded by bright yellow zones were present (fig. 5).

The heart showed fatty infiltrations of the wall of the right ventricle.

The lungs showed patches of bronchopneumonia and areas of bronchiolitis obliterans.

COMMENT

Because of the long-standing presence of normoblasts noted when the patient was in the other institutions, we assumed the following to be the course of events: The patient had the typical pathologic changes seen in Gaucher's disease. Splenectomy was performed in February 1928 because of the hemorrhagic manifestations. One and a half months after splenectomy the anemia disappeared. No early records of the hematologic findings were available. On Jan. 30, 1930, two years after splenectomy, an almost normal hemoglobin value was noted, together with the presence for the first time of normoblasts (fig. 6). From then on, for almost five and a half years, normoblasts were constantly present in the peripheral blood stream. At first their number was small, but they suddenly appeared in great numbers on Dec. 20, 1933 (200 per hundred white blood cells). As soon as this occurred, anemia reappeared and became progressively worse. Six months before death the number

of normoblasts began to diminish. An interesting feature was the appearance of macrocytosis at the end of the patient's life, in April 1935.

The platelets remained normal until the last six months of life, when thrombopenia appeared. Of interest is the fact that the patient had purpura before splenectomy was performed, with a normal platelet count, and that when thrombopenia developed there were no purpuric manifestations, again showing that the number of platelets is not the only factor concerned in purpura.

The white blood cell count did not show any marked changes. At first there was the typical tendency toward leukopenia and lymphocytosis.

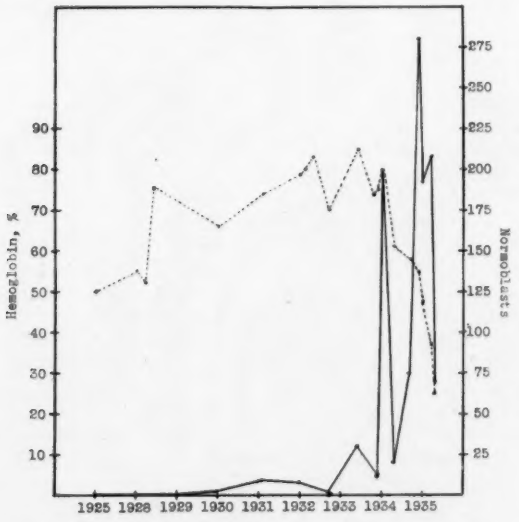

Fig. 6.—Chart showing the relation of hemoglobin to normoblasts. The values along the left ordinate indicate the hemoglobin values, and the values along the right ordinate, the number of normoblasts per hundred white blood cells. The broken line indicates the curve for hemoglobin and the solid line the curve for normoblasts.

Leukocytosis was present postoperatively and during the course of various infectious episodes. The leukocytosis persisted but was due to the large number of nucleated red blood cells. The true white cell count remained low (there was almost leukopenia). Toward the end of life (1935) myelocytes and myeloblasts appeared.

Study of the course of events, then, shows that after splenectomy the anemia disappeared. But this "cure" of the anemia was only apparent. The infiltrations by specific Gaucher tissue in bone marrow, liver and lymphatic glands continued. Because of the resulting mechani-

cal pressure, the bone marrow was functioning under difficulties. The red blood cells persisted and functioned longer because of the removal of the hemolytic activity of the spleen. The essential lesion in the bone marrow progressed. The red blood cells became increasingly immature, the hemoglobin balance being maintained despite these difficulties. In order to maintain this balance, the number of nucleated red blood cells constantly increased. However, a limit was reached, and finally anemia reappeared, despite the normoblasts. Later, even the production of platelets and of white blood cells was affected.

Another interesting finding was hepatic dysfunction, as shown by the abnormal detoxifying function test (bromsulphalein), the urobilinogen in the urine and the macrocytosis of the red blood cells. Anatomically, infiltration of the liver with Gaucher tissue, cirrhosis of the liver and a heterotopic nodule of bone marrow were noted. It seems that the body economy had reverted to embryonal blood formation in the liver to overcome the inability of the bone marrow to maintain hemoglobin equilibrium.

The extensive skeletal involvement is worth emphasizing. The collapsed vertebra and subsequent changes in the contiguous intervertebral disks may present a roentgen picture similar to that in cases of Pott's disease. The osteoplastic changes in the proximal portion of the right humerus are a rarity in Gaucher's disease. The arthritic involvement in early childhood, interpreted as rheumatic fever, reemphasizes the importance of the role of diseases of metabolism in the causation of the arthropathies.

Progress in Internal Medicine

DISEASES OF THE HEART

A REVIEW OF SIGNIFICANT CONTRIBUTIONS MADE DURING 1937

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PHYSIOLOGY AND EXPERIMENTAL PATHOLOGY

Recent improvements in technic have made possible certain studies[1] on the dynamics of the pulmonary circulation in dogs under more nearly normal conditions than heretofore. It has been found that the velocity of the pulse wave in the pulmonary arteries is about the same as that in the aorta at the physiologic pressures existing in each. However, at comparable pressures the velocity is much greater in the pulmonary arteries than in the aorta, which suggests that in low pressure ranges the large pulmonary arteries are less easily distended than is the aorta. Variations in the pressure in the pulmonary arteries with respiration are in the same direction as the variations in the pressure in the systemic arteries, falling in inspiration and rising in expiration. The variations in the pulmonary arteries are probably the direct result of changes in intrathoracic pressure rather than the indirect result of respiratory fluctuations in systemic venous flow. Suddenly increasing the systemic arterial pressure by the administration of epinephrine causes only a slight rise in the pressure in the pulmonary arteries. Thus the right ventricle is spared the sudden strain to which the left ventricle is subjected. This sparing action is due in part to the lowering of systemic venous pressure, in part to the ability of the left ventricle to adjust the force of its ejection to the arterial resistance, but, above all, to the great capacity of the pulmonary bed, enabling it to increase its blood content considerably without a great rise in pressure. Under asphyxial conditions the systemic arterial pressure first rises and then falls. The pressure in the pulmonary arteries and veins does not rise significantly till the systemic arterial pressure starts falling. Thus, under various adverse conditions the weaker, right ventricle is protected by the buffer effect of the pulmonary circuit.

From the Cardiac Clinic of the Massachusetts General Hospital.

1. Johnson, V.; Hamilton, W. F.; Katz, L. N., and Weinstein, W.: Studies on the Dynamics of the Pulmonary Circulation, Am. J. Physiol. **120**:624, 1937.

McMichael,[2] and Sweeney and Mayerson [3] have made careful studies of the postural changes in cardiac output in man. The results of previous investigations have not been uniform, although the majority have indicated that the output decreases after the subject changes from the lying to the sitting or the erect position. This conclusion has been upheld by the aforementioned authors, and their studies have indicated that the amount of the fall is usually from 2 to 30 per cent. Sometimes this fall may be masked by the increased rate of consumption of oxygen usually found when the subject is in the standing position.

Gibson and Evans [4] have used a modification of the dye method in the determination of the plasma and of the total blood volume which has given reliable results. It was found that in normal adults the total volume of blood varies within wide limits. In males the average is 77.7 and in females 66.1 cc. per kilogram of body weight, the difference being due largely to the greater volume of red blood cells in males. It was further found that no relation exists between variations in total blood volume, venous pressure and velocity of blood flow but that the relation of blood volume to height or surface area offers a useful basis for the estimation of the normal blood volume.

Evans and his associates have shown that the working heart utilizes not only dextrose but lactate. Under resting conditions the lactate content of the blood is at its basic level, and its usage by the heart is small. During strenuous muscular exertion, however, the lactate content of the blood is enormously increased, and the heart then uses considerable amounts of that substance and, moreover, uses it in preference to dextrose and in larger amounts. Now it is known that the glycogen content of the heart working under relatively normal conditions is well maintained, and it is a matter of importance to know the relation between the glycogen content of the heart and the sugar and lactate content of the blood.

This problem has been carefully studied by Bogue, Evans and Gregory.[5] They availed themselves of the fact that the continuous

2. McMichael, J.: Postural Changes in Cardiac Output and Respiration in Man, Quart. J. Exper. Physiol. **27**:55, 1937.

3. Sweeney, H. M., and Mayerson, H. S.: Effect of Posture on Cardiac Output, Am. J. Physiol. **120**:329, 1937.

4. Gibson, J. G., and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectrophotometer, J. Clin. Investigation **16**:301, 1937; II. The Relation of Plasma and Total Blood Volume to Venous Pressure, Blood Velocity Rate, Physical Measurements, Age and Sex in Ninety Normal Humans, ibid. **16**:317, 1937.

5. Bogue, J. Y.; Evans, C. L., and Gregory, R. A.: The Source of Heart Glycogen, Quart. J. Exper. Physiol. **27**:27, 1937.

administration of epinephrine rapidly depletes cardiac glycogen.[6] By using dog heart-lung preparations it was found that heart failure rapidly sets in when the glycogen reaches a low level, suggesting that cardiac muscle is incapable of functioning in the absence of glycogen. Addition of lactate after epinephrine depletion of cardiac glycogen leads to no recovery of glycogen, although there is evidence that the lactate is utilized in muscular contraction. Addition of dextrose after glycogen depletion results in considerable restoration of glycogen, showing that this substance is formed from dextrose. Addition of both dextrose and lactate to a glycogen-depleted heart leads to a smaller formation of glycogen than is obtained with dextrose alone, because higher concentrations of lactate depress the utilization of sugar.

The polemic regarding the incidence and significance of blood vessels in human cardiac valves, which began nearly a century ago, still exists. Gross [7] concluded from his extensive studies that blood vessels do not exist in normal valves or that if they do they must be rare. He further concluded that a heart which has so-called normal vascularized valves presents widespread stigmas of healed rheumatic fever. He has cited his reasons for believing that rheumatic fever which has gone on to complete healing is responsible for the formation of these blood vessels.

On the other hand, Wearn and his co-workers [8] have reemphasized that blood vessels are frequently present in normal cardiac valves. The occurrence and distribution of vessels in the valves were studied in 255 hearts revealing no evidence of inflammatory disease and in 78 hearts recognized as being or as having been the seat of inflammation. Sixty-six per cent of the hearts which showed no evidence of inflammatory disease revealed vascularization of one or more valves, about half of which were vascularized beyond the proximal third of the leaflets or cusps. Of especial interest in proving that this vascularization is not the result of unrecognized inflammation was the discovery that in 12 of 49 infants under 1 year of age one or more of the cardiac valves were vascularized beyond the proximal third. Of the hearts which showed evidence of inflammatory disease, 88 per cent revealed vascularization of one or more valves, and 69 per cent revealed one or more valves that were vascularized beyond their proximal third. The frequency with which the various valves are vascularized follows the same sequence in the two groups, the mitral valve having the highest incidence, followed by the tricuspid, pulmonic and aortic valves.

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6. Chang, I.: The Influence of Adrenaline on Cardiac Glycogen, Quart. J. Exper. Physiol. **26**:285, 1937.

7. Gross, L.: Significance of Blood Vessels in Human Heart Valves, Am. Heart J. **13**:275, 1937.

8. Wearn, J. T., and Moritz, A. R.: The Incidence and Significance of Blood Vessels in Normal and Abnormal Heart Valves, Am. Heart J. **13**:7, 1937.

In deciding between these two authoritative reports it is our opinion that the positive findings of Wearn have the advantage over the negative findings of Gross.

Shipley and his associates [9] have found that during the normal growth of the rabbit heart the muscle fibers enlarge and the capillaries multiply, so that a relatively constant capillary supply per unit of tissue is maintained from the time of birth to maturity. In cardiac hypertrophy the muscle fibers enlarge beyond the normal, but the capillaries do not multiply, with the result that the capillary supply per unit of tissue is reduced. It is pointed out that in the hypertrophied heart the relatively decreased capillary supply constitutes an impediment to the exchange of metabolic substances.

MacMahon [10] was prompted to study the problem of normal and pathologic growth of cardiac muscle elements by the observation of an unusually large number of mitoses in the myocardial fibers of the enlarged heart of a 6 month old child. Careful histologic examination of 2 other enlarged hearts, of infants of 12 and 20 months of age, respectively, revealed the presence of mitoses in all stages of nuclear division. Isolated mitotic figures were also observed in the heart of a boy 6 years of age who died several days after the onset of diphtheria. The mitoses were present in muscle fibers which bordered zones of destruction. MacMahon's observations are of unusual interest as many investigators have painstakingly searched throughout the myocardium of patients with cardiac hypertrophy without finding any positive evidence, in the form of mitoses, of proliferation of muscle fibers.

Comeau [11] has described 2 cases of diffuse parietal endocardial sclerosis and has reviewed the cases described previously.

Golden and Brams [12] were able to find in the medical literature of the last century only 38 reports of cases in which the heart weighed 1,000 Gm. or more. Details of 9 additional cases are given. Of especial interest is the fact that the enlargement in only 1 of these 9 was associated with pericardial adhesions, while about half of those previously reported were supposedly due to pericardial adhesions alone or in combination with valvular disease. Aortic regurgitation of syphilitic origin and aortic stenosis of rheumatic origin are the common causes of massive cardiac enlargement aside from adhesive pericarditis.

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9. Shipley, R. A.; Shipley, L. J., and Wearn, J. T.: The Capillary Supply in Normal and Hypertrophied Hearts of Rabbits, J. Exper. Med. **65**:29, 1937.

10. MacMahon, H. E.: Hyperplasia and Regeneration of the Myocardium in Infants and in Children, Am. J. Path. **13**:845, 1937.

11. Comeau, W. J.: Diffuse Parietal Endocardial Sclerosis: Review of the Literature and Report of Two Cases, Am. J. Path. **13**:277, 1937.

12. Golden, J. S., and Brams, W. A.: Extreme Cardiac Enlargement, Am. Heart J. **13**:207, 1937.

METHODS, SYMPTOMS AND SIGNS

Kerr and his associates [13] have devised a modified stethoscope, termed the symballophone, which can be used to determine the point of origin of sounds and the direction of propagation. Preliminary observations have indicated that this device will be useful in studying heart sounds and murmurs.

Sprague [14] has reviewed the subject of the mechanism of production of cardiac murmurs. Of especial interest is the discussion of certain factors modifying the audibility of murmurs. For example, the extreme softness or absence of a diastolic murmur of aortic regurgitation in many instances of aortic stenosis is probably due to the damping effect of the cone-shaped valves directed against the current, augmented by the damping effect of the funnel-shaped opening into the left ventricle from the aorta. Again, in instances of mitral stenosis associated with high blood pressure in the left auricle, the mitral regurgitant murmur may be greatly damped because the entrance of a jet of fluid into a chamber where the pressure is high causes less murmur. The question of functional murmurs has been ably discussed by the author.

Lian [15] has described 3 cases in which continuous murmurs were best heard in the second or third intercostal space to the right of the sternum. He has given his reasons for believing that these murmurs originated in the superior vena cava, probably as a result of compression of this vessel, and that they were analogous to the continuous murmurs sometimes heard over the jugular vein in the neck. Lian [16] has further described 2 cases in which continuous murmurs were heard over the right interscapulovertebral space and has explained their presence as being due probably to compression of a pulmonary vein. We are reminded of a case in which a loud continuous murmur was heard over the lower right portion of the thorax posteriorly; necropsy did not reveal anything which would serve as an explanation.

Dressler [17] has described, with considerable accuracy, the pulsations of the wall of the chest as they are found normally and in certain

13. Kerr, W. J.; Althausen, T. L.; Bassett, A. M., and Goldman, M. J.: The Symballophone: A Modified Stethoscope for Lateralization and Comparison of Sounds, Am. Heart J. **14**:549, 1937.

14. Sprague, H. B.: The Mechanism of the Production of Heart Murmurs, in Kerr, W. J.: Modern Concepts of Cardiovascular Disease, New York, American Heart Association, 1937, vol. 6.

15. Lian, C.: Le souffle continu cave supérieur, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:1088, 1937.

16. Lian, C.: Le souffle veineux continu de l'espace interscapulo—vertébral droit, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:1100, 1937.

17. Dressler, W.: Pulsations of the Wall of the Chest: I. General Consideration, Arch. Int. Med. **60**:225 (Aug.) 1937; II. Pulsations Associated with Aortic

types of heart disease. Although it is good to have on record a correct analysis of these pulsations, the practical value of such knowledge is small.

ROENTGENOLOGY

Roesler [18] has written the most authoritative book in the English language on the subject of cardiovascular roentgenology. This book has been adequately reviewed in many medical journals.

One of the most important studies that have been reported during the past year was Palmer's [19] on the development and progression of cardiac enlargement in heart disease as determined from serial teleroentgenograms. The material has been well arranged and concisely dealt with and is of great practical value. Of especial interest were the findings in cases of hydrothorax due to heart failure, in which, contrary to expectation, appreciable cardiac displacement was not found to occur. About the only statement with which we are not in agreement is that in coronary disease, enlargement of the heart may be due to chronic myocardial ischemia alone. Of the 5 cases illustrating this conception, complications were present in every one, coronary thrombosis in 4 and chronic congestive failure in 1 other.

The more significant conclusions are worth quoting:

> In the majority of cases of congestive failure no decrease was noted in the size of the heart after clinical improvement. When regression did occur, it was usually general, involving both borders, but chiefly the right auricle and superior vena cava.
>
> Although the evidence is yet inconclusive, some degree of permanent enlargement probably often remains as a result of, and after recovery from, prolonged bouts of congestive failure, such as are found in mitral stenosis and in hyperthyroidism with auricular fibrillation. Short bouts of failure, e. g., in prolonged attacks of paroxysmal tachycardia, are without permanent effect on the size of the heart.
>
> No example could be found of a right-sided hydrothorax in failure causing displacement of the right border of the heart, or of the heart as a whole, to the left. On the contrary, the right border was often moved to the right, apparently influenced by elevation of the diaphragm.

Regurgitation, ibid. **60**:437 (Sept.) 1937; III. Pulsations Associated with Tricuspid Regurgitation, ibid. **60**:441 (Sept.) 1937; IV. Pulsations Associated with Adhesive Pericardial Disease, ibid. **60**:654 (Oct.) 1937; V. Pulsations Associated with Mitral Regurgitation and Aneurysmal Dilatation of the Left Auricle, ibid. **60**:663 (Oct.) 1937.

18. Roesler, H.: Clinical Roentgenology of the Cardiovascular System, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

19. Palmer, J. H.: The Development of Cardiac Enlargement in Disease of the Heart: A Radiological Study, Medical Research Council, Special Report Series, no. 222, London, His Majesty's Stationery Office, 1937.

Enlargement of the heart in paroxysmal tachycardia is referable to the supervention of congestive failure in a prolonged attack, for otherwise it is minimal or absent.

Established auricular fibrillation and flutter usually, but not always, cause enlargement. When enlargement develops it is almost invariably associated with signs of congestion in one or both of the pulmonary and systemic circuits. Radiologically the enlargement is found to involve most frequently the right auricle, superior vena cava, pulmonary arc, and less often the left auricle. The enlargement in these arrhythmias is probably bound up with and indicative of coincident failure.

Wherever the heart assumes a so-called characteristic radiological shape, notably in valvular lesions, the local changes in chamber size involved in the determination of this shape are the first changes to take place. Further enlargement of the X-ray shadow tends to be more or less equally distributed on all cardiac borders (general enlargement), thus preserving, though in a modified form, the shape peculiar to the disease. After the apex has reached the left axilla, progressive enlargement continues to the right.

General enlargement was the type most often encountered during the investigation. It was due, both in the later stages of slowly developing enlargement, and in the more rapid enlargement associated with such conditions as the onset of auricular fibrillation, chiefly to the participation of more than one chamber in the process.

Another factor tending to bring about an appearance of general enlargement is the ability of the fibrous pericardium so to distribute intra-pericardial tension by causing alteration in position of the heart in the pericardial sac that localised increase in cardiac size may result in displacement of all borders of the radiological shadow in some measure.

The impression was gained that there is in young persons a greater tendency than in older ones towards development of enlargement under similar conditions. In this connection the single case of rapid and great hypertrophy in a child with hypertension is significant.

In essential hypertension cardiac enlargement appears to develop simultaneously and equally with the gradual rise of blood-pressure to a permanent fixed level during months or years. Progressive enlargement in uncomplicated cases does not easily occur after the blood-pressure level has become stabilized.

Most examples of progressive cardiac enlargement were seen in diseases known to be progressive in the pathological sense, chiefly rheumatic valvular lesions and coronary sclerosis. This observation, taken in conjunction with the findings that enlargement often failed to progress in stabilized hypertension, in syphilitic aortic incompetence where there was apparent clinical arrest of the lesion, and in gross aneurysm of the myocardial wall following coronary thrombosis, lends support to the view that enlargement evoked in response to a certain burden does not progress if the burden is not increased. It may be assumed that whenever progressive enlargement is discovered either the original lesion is progressive in character or some new factor has become operative.

So-called acute dilatation of the heart, that is, gross enlargement developing in a few hours or days, is rare. It never seems to arise at the onset or during the course of abnormal rhythms where it might be expected, nor in the later stages of chronic cardiac disease. The nearest approach to it seems to be the rapid enlargement shown by Dorner to develop within a few days in severe diphtheria.

ELECTROCARDIOGRAPHY

Joint recommendations [20] for the use of a single precordial lead (called lead IV) as a routine have been made by committees acting for the American Heart Association and the Cardiac Society of Great Britain and Ireland. In addition to these joint recommendations the American committee [21] has had published a more extended account with reference to multiple precordial leads and to the theoretic considerations on which these recommendations are based.

For ordinary use the following recommendations apply: The apical electrode should be circular and between 2 and 3 cm. in diameter. It should be placed over the extreme outer apical border of the heart as determined by palpation. If the palpation is unsatisfactory the apical border of the heart should be determined by some other means. The paired electrode preferably should be placed on the left leg, in which case the lead is designated as IV F. If other locations for the indifferent electrode are selected, they should carry the designation B for interscapular region, R for right arm and L for left arm. Galvanometric connections should be made in such a way that the relative positivity of the apical electrode is represented in the electrocardiogram by an upward deflection. The deflections in the precordial lead should be designated P, Q, R, S and T, respectively, just as in the case of the limb leads. Normally the QRS wave of this new lead IV is diphasic, with an upright first phase, R, and the T wave is upright. The report of the American committee should be consulted for details concerning the employment of multiple chest leads.

Gilson and Bishop [22] have presented a convincing argument that the dipole theory of tissue potentials, which attempts to explain the genesis of the electrocardiogram, is inadequate. They have stated the opinion that the classic hypothesis, or the hypothesis of so-called negativity, should not be abandoned on the basis of arguments offered in support of the dipole theory.

Katz [23] has presented a summary of his views in regard to the genesis of the electrocardiogram. It is especially emphasized that the electrocardiogram is a record of events in favored rather than in all regions

20. Standardization of Precordial Leads: Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland, Am. Heart J. **15**:107, 1938. Standardization of Precordial Leads, J. A. M. A. **110**:395 (Jan. 29) 1938.

21. Standardization of Precordial Leads: Supplemental Report, J. A. M. A. **110**:681 (Feb. 26) 1938.

22. Gilson, A. S., and Bishop, G. H.: The Effect of Remote Leads upon the Form of the Recorded Electrocardiogram, Am. J. Physiol. **118**:743, 1937.

23. Katz, L. N.: Concerning a New Concept of the Genesis of the Electrocardiogram, Am. Heart J. **13**:17, 1937.

of the heart. Currents due to injury and affecting these favored regions are revealed, but those in other areas may be missed.

Abramson and Jochim [24] have stated that they are not in agreement with current concepts regarding the impulse spread in the ventricles. Their experimental data have justified the belief that the impulse does not leave the subendocardial Purkinje network to spread out and over the muscle itself but remains in this network and excites the muscle in numerous places almost simultaneously; also, that the impulse spread has no relation to the direction of the muscle bundles. These experimental data confirm the anatomic observations of Abramson and Margolin.[25]

We feel that despite wide differences in opinion regarding the intimate nature of the electrocardiogram, its clinical value remains about the same because clinical electrocardiography is largely empiric. These differences also form a strong argument for the importance of continuing to collect such empiric clinical data.

Robb and Robb [26] have reemphasized that when the R peaks of the electrocardiogram are out of phase, there exists no satisfactory method for calculating the electrical axis. Thus, unless E_2 equals E_1 plus E_3, the R peaks are out of phase, and each R may have an axis of its own that differs about 50 to 100 degrees from those of the others. It is suggested that in these instances the method used in calculating the axis should be indicated.

Lambert [27] stated that he was persuaded, on the basis of animal experimentation and clinical observation, that certain alterations in the P wave and in the PR segment may occur as a result of ischemia of the auricular musculature. These alterations are, notably, a notching or inversion of the P wave and depressions of the PR segment which are analogous to changes in the ST segment. The significance of such alterations is lost, however, unless normal sinus rhythm is present. Also certain normal variations of the P wave must be kept in mind, such as slight notching in any lead and inversion in lead III.

Barker, Johnson and Wilson,[28] and Hegglin and Holzmann [29] have reemphasized the fact that the Q to T interval of the electrocardiogram

24. Abramson, D. I., and Jochim, K.: The Spread of the Impulse in the Mammalian Ventricle, Am. J. Physiol. **120**:635, 1937.

25. Abramson, D. I., and Margolin, S.: A Purkinje Conduction Network in the Myocardium of the Mammalian Ventricles, J. Anat. **70**:250, 1936.

26. Robb, R. C., and Robb, J. S.: The Electrical Axis in Simultaneous Leads: I. Factors Increasing the Dispersion of Normal Values, Am. Heart J. **14**:588, 1937.

27. Lambert, J.: Les altérations d'origine coronarienne du complexe électrocardiographique auriculaire: Etude expérimentale et clinique, Arch. d. mal. du cœur **30**:3, 1937.

28. Barker, P. S.; Johnson, F. D., and Wilson, F. N.: The Duration of Systole in Hypocalcemia, Am. Heart J. **13**:82, 1937.

is abnormally prolonged in the presence of abnormally low levels of calcium in the blood serum. This, as an incidental finding, may lead to the recognition of otherwise unsuspected conditions associated with hypocalcemia.

Mussen [30] found that in rabbits, after orthostatic collapse or after the administration of histamine in large doses, there regularly appeared in the electrocardiogram lowering of the ST segment in leads I and II which was sometimes associated with inversion of the T waves. Histologic examination of the cardiac muscle of animals which survived the histamine or orthostatic collapse revealed disseminated anoxemic necrosis.

Akesson [31] has reported the finding of an inverted T wave in lead II or III of the electrocardiograms of apparently normal persons which changed to normal when there was a shift from the upright to the recumbent position. He concluded that this apparent abnormality, which suggests coronary disease, may be dependent on relative myocardial ischemia due to what he has called orthostatic arterial insufficiency.

CARDIAC ARRHYTHMIAS

Dumitresco-Mante [32] has studied the problem of icteric bradycardia. From clinical and experimental observations he concluded that icteric bradycardia is neurogenic, resulting from disequilibrium between the vagus and the sympathetic nerves but with the vagal tonus predominating. This disequilibrium is believed to be due to the increase in the content of choline and potassium in the blood rather than any change in concentration of the bile salts or calcium.

Harvey [33] has pointed out that in many instances of paroxysmal tachycardia the auricular complex is not clearly discernible in the three conventional electrocardiographic leads and for this reason the cardiac rhythm cannot be determined with certainty. Cases are presented illustrating the manner in which this difficulty was overcome with the aid of esophageal leads.

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29. Hegglin, R., and Holzmann, M.: Die klinische Bedeutung der verlängerter QT-Distanz (Systolendauer) im Elektrokardiogramm, Ztschr. f. klin. Med. **132**:1, 1937.

30. Mussen, H.: Ueber Coronarinsuffizienz nach Histamin-Collaps und nach orthostatischen Collaps, Beitr. z. path. Anat. u. z. allg. Path. **99**:329, 1937.

31. Akesson, S.: Ueber Veränderungen des Elektrokardiogramms bei orthostatischer Zirkulationsstörung, Upsala läkaref. förh. **41**:383, 1936.

32. Dumitresco-Mante, M.: La bradycardie et le syndrome humoral au cours des ictères du type catarrhal, J. de physiol. et de path. gén. **35**:14 and 416, 1937.

33. Harvey, A. McG.: The Origin of Paroxysmal Tachycardias as Determined by the Esophageal Electrocardiogram, Ann. Int. Med. **11**:57, 1937.

We suggest that in many cases, at least, this technic is unnecessary because a well defined auricular wave may be obtained in a precordial lead by placing one electrode in the third or fourth interspace just to the right of the sternum.

Campbell [34] and Lyon [35] have reported observations on patients with paroxysmal tachycardia with a very rapid heart rate. The nature of these arrhythmias is often difficult to determine even from electrocardiograms. Usually the paroxysms consist of either auricular tachycardia or auricular flutter and are more likely to be associated with a diseased than with a healthy heart. Cardiac symptoms usually appear unless the attack is short lived.

Brill [36] has reviewed in a concise manner the knowledge concerning auricular fibrillation from a clinical aspect.

Sprague [37] has described an unusual instance of auricular fibrillation and bundle branch block. After the administration of digitalis the auricular fibrillation ceased, but the bundle branch block persisted and was associated with a short PR interval. This strange association has been shown to occur in apparently healthy persons, and the importance of its proper recognition is apparent.

Comeau [38] has critically reviewed the medical literature on recurrent complete heart block alternating with normal conduction and accompanied by the Adams-Stokes syndrome. Two additional cases are reported, and certain practical and therapeutic considerations are emphasized.

Hoff and Nahum [39] have analyzed the cardiac irregularities produced in rabbits after the administration of calcium salts. In the nonanesthetized animal, after the injection of 20 cc. of a 10 per cent solution of calcium chloride, auricular fibrillation developed in each instance, as well as frequent premature beats and various grades of auriculoventricular block. Previous atropinization prevented auriculoventricular block and auricular fibrillation but promoted the development of ventricular extrasystoles and occasionally precipitated ventricular

34. Campbell, M.: Paroxysmal Tachycardia in Infants, Guy's Hosp. Rep. **87**: 205, 1937.

35. Lyon, J. A.: Excessively Rapid Heart Rates: Report of a Case with Autopsy, J. A. M. A. **108**:1393 (April 24) 1937.

36. Brill, I. C.: Auricular Fibrillation: The Present Status, with a Review of the Literature, Ann. Int. Med. **10**:1487, 1937.

37. Sprague, H. B.: Auricular Fibrillation and Bundle Branch Block in an Apparently Normal Heart: A Case Report, Internat. Clin. **1**:187, 1937.

38. Comeau, W. J.: Paroxysmal Heart Block Alternating with Normal Rhythm and Conduction, Am. J. M. Sc. **194**:43, 1937.

39. Hoff, H. E., and Nahum, L. H.: An Analysis of the Cardiac Irregularities Produced by Calcium and Their Prevention by Sodium Amytal, J. Pharmacol. & Exper. Therap. **60**:425, 1937.

tachycardia and ventricular fibrillation. Sodium amytal in narcotic doses was found to suppress all cardiac irregularities due to calcium chloride and to prevent arrest of the heart, which is probably to be attributed to the depression of both vagal and sympathetic activity.

CONGENITAL HEART DISEASE

Yater and Shapiro [40] have reported a typical example of Ebstein's disease and have summarized the data regarding 15 previously reported cases. This disease is a rare congenital anomaly, consisting essentially of downward displacement of the tricuspid valve in an otherwise completely developed heart. Commonly associated findings are patent foramen ovale and enlargement of the right auricle.

Clinical diagnosis of this disease seems impossible, although it may be suspected. The enlargement of the heart is not characteristic. Usually there is a loud systolic murmur heard best at the level of the third or fourth intercostal space near the sternum; occasionally both systolic and diastolic murmurs are heard with or without an accompanying thrill. The pulmonic second sound is usually not accentuated. Cyanosis and clubbing of the fingers may or may not be present. Signs of tricuspid insufficiency usually appear only when congestive heart failure is precipitated. This condition is compatible with long life, and pulmonary tuberculosis appears as a frequent complication.

RHEUMATIC HEART DISEASE

Etiologic Factors.—There has been further evidence against the concept that rheumatic fever may be due to the combined influence of vitamin C deficiency and infection. Finkle,[41] and Faulkner and Taylor,[42] who have studied the relation of vitamin C and infection, have found no evidence that vitamin C deficiency has a causal relation to any pathologic condition other than scurvy and that the effect of rheumatic fever on vitamin C metabolism appears to be the same as that of other infectious diseases. McBroom and his associates [43] have studied acute scurvy produced in guinea pigs with and without superimposed infection. It was concluded that although scurvy may indirectly be a factor

40. Yater, W. M., and Shapiro, M. J.: Congenital Displacement of the Tricuspid Valve (Ebstein's Disease): Review and Report of a Case with Electrocardiographic Abnormalities and Detailed Histologic Study of the Conduction System, Ann. Int. Med. **11**:1043, 1937.

41. Finkle, P.: Vitamin C Saturation Levels in the Body in Normal Subjects and in Various Pathological Conditions, J. Clin. Investigation **16**:587, 1937.

42. Faulkner, J. M., and Taylor, F. H. L.: Vitamin C and Infection, Ann. Int. Med. **10**:1867, 1937.

43. McBroom, J.; Sunderland, D. A.; Mote, J. R., and Jones, T. D.: Effect of Acute Scurvy on the Guinea-Pig Heart, Arch. Path. **23**:20 (Jan.) 1937.

in lowering the general resistance of the body to infection, there is as yet no evidence of a direct causal relation between this disease and rheumatic fever.

Eagles and his co-workers [44] have presented evidence which, they concluded, supports the possibility that rheumatic fever is due to a virus infection. Suspensions of particles bearing a close resemblance to elementary bodies of known virus infection were prepared from exudates obtained from patients with acute rheumatic fever, rheumatoid arthritis and chorea. These particles were found to be agglutinated by serum from patients suffering from the corresponding disease. Cross agglutination occurred within the whole group with sufficient regularity to point to an interrelation. Various control suspensions were in no case agglutinated by any of the known serums. Agglutination of suspensions of exudates from patients with rheumatic fever by serum from patients with rheumatic fever occurs in various types of the disease in the active stage and also when it has become inactive. The number of serums giving a positive agglutination reaction is about equal to the number of those showing no agglutination. When individual serums were tested at intervals throughout several weeks, it was not possible to correlate the presence or absence of agglutination with any definite phase of the clinical condition. We wish to add that other investigators, using essentially the same material and methods, have not been able to substantiate these results.

A number of interesting reports [45] have appeared showing the influence of climate and race on rheumatic heart disease. Of especial interest is Paul and Dixon's survey among American Indian school children in northern and southern localities. It was found that in the cold though relatively dry climate of the northwestern localities the incidence of rheumatic heart disease is high (4.5 per cent), whereas in the warm and dry climate of the southwestern localities the incidence is low (0.5 per cent). In localities between these extremes the incidence of rheumatic heart disease is 1.9 per cent. Furthermore, it is probable that the clinical course of the disease is milder in southwestern than in northern localities. Even allowing for possible sources of error, it is apparent that the incidence of rheumatic heart disease is many times greater in the North than in the South.

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44. Eagles, G. H.; Evans, P. R.; Fisher, A. G. T., and Keith, J. D.: A Virus in the Aetiology of Rheumatic Diseases, Lancet **2**:421, 1937.

45. Paul, J. R., and Dixon, G. L.: Climate and Rheumatic Heart Disease: A Survey Among American Indian School Children in Northern and Southern Localities, J. A. M. A. **108**:2096 (June 19) 1937. Chang, F. C., and Dieuaide, F. R.: Clinical Study of Rheumatic Fever, Chinese M. J. **51**:581, 1937. Maddox, K.: Metropolitan and Rural Incidence and Distribution of Acute Rheumatism and Rheumatic Heart Disease in New South Wales, M. J. Australia **1**:394, 1937.

Pathologic Changes.—Waaler,[46] in a study of the superior vena cava at its entrance into the right auricle, observed rheumatic lesions in 8 of 73 cases of rheumatic carditis. These lesions have some of the features of the lesions of auricular rheumatic endocarditis and also of rheumatic aortitis which have been described. In 8 additional cases hyaline plaques were observed, but it was undecided whether they represented the final and healed stage of the acute rheumatic lesions or whether they were sclerotic.

Gross and Silverman[47] have studied the inflammatory changes observed in the aortic commissures in 70 cases of rheumatic fever. The pathogenesis of these commissural lesions was discussed, and it appears that even though the original infection may reach the aortic ring through several routes, in most instances the inflammatory granulation tissue passes from the pericardial mantle through the aortic root, wedge and annulus to reach the aortic ring.

Rae[48] has described some unusual pathologic changes seen in a young child who died of acute rheumatic fever with pancarditis. Marked acute inflammatory lesions of a proliferative, degenerative and necrotic character involved the main coronary arteries. Large aneurysmal dilatations in the right coronary artery and in the descending branch of the left coronary artery were observed. Thrombosis occurred in the right coronary aneurysm without causing myocardial infarction. Although the possibility that these aneurysms were of congenital origin cannot be denied, it is much more likely that they resulted from rheumatic infection.

Massell and his associates[49] demonstrated that the subcutaneous injection of the patient's own blood, with subsequent frictional pressure, resulted in the appearance of a nodule in the immediate area in 37 of 82 subjects with rheumatic fever and chorea. A definite relation was found between the activity of the process of rheumatic fever and the induction of nodules. Thus, the appearance of nodules in 90 per cent of the patients with clinically active rheumatic fever and in 50 per cent of those with only laboratory evidence of active rheumatic fever was in striking contrast to their appearance in only 14 per cent of the subjects without evidence of active rheumatic fever and in 14 per cent of the

46. Waaler, A.: Morphological Changes in the Superior Vena Cava and Right Auricle in Rheumatic Heart Disease, Am. J. Path. **13**:855, 1937.

47. Gross, L., and Silverman, G.: The Aortic Commissural Lesion in Rheumatic Fever, Am. J. Path. **13**:389, 1937.

48. Rae, M. V.: Coronary Aneurysms with Thrombosis in Rheumatic Carditis, Arch. Path. **24**:369 (Sept.) 1937.

49. Massell, B. F.; Mote, J. R., and Jones, T. D.: The Artificial Induction of Subcutaneous Nodules in Patients with Rheumatic Fever, J. Clin. Investigation **16**:125, 1937.

subjects with chorea. A nodule appeared in only 1 of the 34 control subjects. The duration of these induced nodules varied from a few weeks to several months, and the clinical course was comparable to that when nodules appeared spontaneously.

Mote and his associates [50] found that there is a great similarity of pathologic structure between induced and spontaneously occurring nodules of similar age.

Collins [51] has reported his studies on the examination and comparison of nodules from patients with rheumatoid arthritis and rheumatic fever and nodules arising as the result of injury alone. Certain differences were noted, but he concluded that there was enough evidence to postulate either a close pathologic relation or a common etiologic factor of the nodules in rheumatoid arthritis and those in rheumatic fever.

Course and Prognosis.—A number of reviews and statistical analyses [52] have appeared bearing on the clinical course of rheumatic fever. Little that is new has been added. One point that probably should be emphasized even more strongly than heretofore is the great tendency to recurrences after the initial attack of acute rheumatism in children. They should be kept under close observation at least until past puberty, when the tendency toward recurrence is decreased.

Complications.—Graef and his co-workers [53] have studied carefully the problem of auricular thrombosis in hearts showing evidence of rheumatic disease. This complication was present in 24 of the 178 hearts studied. Of the 24 instances of auricular thrombosis, congestive heart failure was associated in 21, auricular fibrillation in 18, mitral stenosis in 18, active rheumatic carditis in 14 and macroscopic auricular scarring in 22. Although all these factors appear to favor the development of auricular thrombi, the persistence of active inflammation appears to be the chief one.

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50. Mote, J. R.; Massell, B. F., and Jones, T. D.: The Pathology of Spontaneous and Induced Subcutaneous Nodules in Rheumatic Fever, J. Clin. Investigation **16**:129, 1937.

51. Collins, D. H.: Subcutaneous Nodule of Rheumatoid Arthritis, J. Path. & Bact. **45**:97, 1937.

52. Cushing, H. B.: Rheumatic Fever and Heart Disease in Children, Canad. M. A. J. **37**:311, 1937. Conner, L. A.: Comments upon Certain Aspects of Rheumatic Fever and Rheumatic Heart Disease, New England J. Med. **217**:503, 1937. Coburn, A. F., and Moore, L. V.: The Independence of Chorea and Rheumatic Activity, Am. J. M. Sc. **193**:1, 1937. Roth, I. R.; Lingg, C., and Whittemore, A.: Heart Disease in Children, Am. Heart J. **13**:36, 1937. Leonard, M.: Puberty and Prognosis in Rheumatic Fever, ibid. **14**:192, 1937.

53. Graef, I.; Berger, A. R.; Bunim, J. J., and de la Chapelle, C. E.: Auricular Thrombosis in Rheumatic Heart Disease, Arch. Path. **24**:344 (Sept.) 1937.

Levine and White [54] have reported their findings regarding pulmonary infarction as a complication of severe disease of the mitral valve. Five fatal cases have been reported in detail, including the necropsy data. Analysis of the incidence of this complication in a series of 52 cases of mitral stenosis showed that pulmonary infarction occurred in 61 per cent of the 23 cases in which there was congestive failure and in only 7 per cent of the cases in which congestive failure was not present. In a comparative group of 82 cases of hypertension there were 39 instances of congestive failure, in 21 of which there was pulmonary infarction. Pulmonary infarction is a common complication of congestive failure from any cause but particularly when mitral stenosis is present; it is often overlooked and may account for the inability of the failing heart to respond to treatment.

Harvier and his associates [55] have discussed the occurrence of functional pulmonary regurgitation as a complication of mitral stenosis. The difficulties in clinical diagnosis have been emphasized, especially the difficulty in differentiating the Graham Steell murmur from that of aortic regurgitation. A case has been described wherein roentgen kymography confirmed the clinical interpretation that pulmonary rather than aortic regurgitation was present. A plea has been made for the further employment of this diagnostic method in all such cases.

Contratto and Levine [56] made a study of 180 patients with aortic stenosis, unassociated with any other significant valvular disease, 53 of whom were examined post mortem. They concluded that the etiologic factor in most cases was previous rheumatic infection. In about half the cases an aortic diastolic murmur was not audible. Angina pectoris occurred in nearly a fourth of the cases, and the presence of normal coronary vessels in 2 of the young patients and only minimal atheroma in the vessels of some of the others that had angina pectoris strongly suggested that the deformity of the valve itself was in some way responsible. The frequent absence (19 of the 41 instances) of aortic insufficiency in this group of patients with angina pectoris was of especial interest.

Treatment.—Sadow and her co-workers [57] have shown that a diet that has a high caloric value and that is optimal in all nutritional elements is beneficial in the treatment of rheumatic fever. This conclusion

54. Levine, H. B., and White, P. D.: Pulmonary Infarction Complicating Severe Disease of the Mitral Valve, Arch. Int. Med. **60**:39 (July) 1937.

55. Harvier, P.; Mallarmé, J., and Ledoux-Lebard, G.: Artérite pulmonaire avec insuffisance fonctionelle de l'orifice pulmonaire dans le rétrécissement mitral à propos d'un cas avec radiokymographie, Paris méd. **1**:397, 1937.

56. Contratto, A. W., and Levine, S. A.: Aortic Stenosis, with Special Reference to Angina Pectoris and Syncope, Ann. Int. Med. **10**:1636, 1937.

57. Sadow, S. E.; Hubbard, J. P., and Jones, T. D.: A Dietary Study in Rheumatic Fever, New England J. Med. **217**:170, 1937.

was based on the fact that the gain in weight with such a diet was greater than with the usual hospital diet although no observable difference in the course of the disease was seen.

Barnacle, Ewalt and Ebaugh,[58] and Kendell and Simpson[59] have reported favorably on the treatment of chorea with artificial fever. This has confirmed the favorable results previously reported.

Levy and Golden[60] have reported favorable results of roentgen therapy in active rheumatic heart disease. Their experience covered 48 patients observed during eleven and one-half years. The impression was gained that low grade infections respond better to irradiation than the more acute types and that patients with congestive failure are poor subjects for this form of therapy. Patients with cardiac pain are uniformly helped, save those with aortic regurgitation. The manner in which improvement is initiated is unknown. The technical method has been described. We feel, however, that it is difficult to judge the value of any such therapeutic measure on the basis of the rate of convalescence from a low grade rheumatic infection, which is so notoriously variable in its course.

BACTERIAL ENDOCARDITIS

Keefer[61] has studied a group of 15 patients with active bacterial endocarditis but without bacteremia. There was no essential difference in the clinical course recorded for these patients and that for a comparable group of patients with bacteremia except that the nonbacteremic patients were more likely to have renal insufficiency as an outstanding feature of their illness. A significant parallel was drawn between the endocarditis in horses which have been immunized against pneumococci and the bacterial endocarditis of patients whose blood is sterile on culture. The high antibody titer in the horse blood favors the localization of bacteria but at the same time destroys bacteria released into the blood stream. Keefer has presented presumptive evidence that an analogous condition obtains in man.

Gross and Fried[62] have described the macroscopic and microscopic appearance of the heart in 42 cases of subacute bacterial endocarditis and in 28 cases of acute bacterial endocarditis. Seventy-five per cent

58. Barnacle, C. H.; Ewalt, J. R., and Ebaugh, F. G.: Artificial Fever Treatment of Chorea: A Two Year Study, J. A. M. A. **109**:111 (July 10) 1937.

59. Kendell, H. W., and Simpson, W. M.: Artificial Fever Therapy of Sydenham's Chorea, Ohio State M. J. **33**:1097, 1937.

60. Levy, R. L., and Golden, R.: Roentgen Therapy of Active Rheumatic Heart Disease: A Summary of Eleven Years' Experience, Am. J. M. Sc. **194**:597, 1937.

61. Keefer, C. S.: Subacute Bacterial Endocarditis: Active Cases Without Bacteremia, Ann. Int. Med. **11**:714, 1937.

62. Gross, L., and Fried, B. M.: The Role Played by Rheumatic Fever in the Implantation of Bacterial Endocarditis, Am. J. Path. **13**:769, 1937.

of the hearts had been the seat of a rheumatic process, and Aschoff bodies were encountered in approximately 30 per cent. Reasons have been given which indicate that activity of a rheumatic infection is not a necessary precursor to the development of bacterial endocarditis; much more important are the formation of eosinophilic necrosis of the valvular closure line and the thrombotic, proliferative and necrotic changes at these sites. It did not appear to the authors that the vascularization occurring in rheumatic valves plays an appreciable role in the implantation of bacterial endocarditis.

Chester [63] has reported a case that is of unusual interest because it is the first recorded instance of apparent recovery from subacute bacterial endocarditis of a patient with patency of the ductus arteriosus.

ARTERIAL HYPERTENSION

Pathogenesis.—It has been shown repeatedly that renal ischemia, produced by constricting the main renal arteries, as suggested by Goldblatt, will cause arterial hypertension. Experimental constriction of one renal artery results in temporary hypertension, and constriction of both results apparently in permanent hypertension. The amount of constriction determines the degree of hypertension. Thus slight constriction generally results in a benign form, usually without evidence of renal impairment; moderate or severe constriction results in a malignant form, with much renal impairment, and complete occlusion causes little or no rise in blood pressure. Many other methods which reduce the renal function and which have been recently tried [64] do not result in a permanent increase in blood pressure. Constriction of splenic and of femoral vessels has no effect on blood pressure.

The exact mechanism whereby the kidney produces the rise in blood pressure in experimental hypertension is still unsolved, although it is the immediate result of the narrowing of the arterioles; the blood volume, blood viscosity and cardiac output remain normal. The problem thus appears to be the same as it is in essential hypertension. It was at first thought that the nervous system might play an essential role, with the reflex stimulation coming from the ischemic kidney. However, this does not seem likely,[65] since denervation of the kidneys, section of

63. Chester, W.: Patent Ductus Botalli with Subacute Bacterial Endocarditis and Recovery, Am. Heart J. **13**:492, 1937.

64. Scarff, R. W., and McGeorge, M.: Experimental Renal Lesions and Blood Pressure in Rabbits, Brit. J. Exper. Path. **18**:59, 1937. Konzett, H., and Unna, K.: Die Blutdruckänderungen nach Ausschalten von Nierenarterien an Hunden, Arch. f. exper. Path. u. Pharmakol. **186**:694, 1937.

65. Goldblatt, H.; Gross, J., and Hanzel, R. F.: Studies on Experimental Hypertension: II. The Effect of Resection of Splanchnic Nerves on Experimental Renal Hypertension, J. Exper. Med. **65**:233, 1937. Goldblatt, H.: Studies on

(Footnote continued on next page)

the anterior nerve roots, total sympathectomy and denervation of the heart combined with total sympathectomy do not abolish the hypertension. Furthermore, it has been shown [66] that constriction of the artery of a transplanted kidney, free from any possible nervous connections, leads to an increase in blood pressure.

The results of Goldblatt's [67] recent experiments, which were given in a preliminary report, suggested that the mechanism of this type of hypertension is primarily humoral and of renal origin. Thus, varying degrees of constriction of both main renal arteries are followed by hypertension while bilateral nephrectomy is not. This difference has been attributed to the absence of a hypothetic effective substance when the kidneys are absent. The constriction or occlusion of both renal arteries, when accompanied by occlusion of the renal veins, is not followed by the development of hypertension. This has been interpreted as being due to interference with the entrance of the hypothetic effective substance into the circulation. When hypertension is produced by constriction of one or both renal arteries, release of the constriction is followed, in a greater or lesser time, by return of the pressure to normal. Excision of the ischemic kidney at the height of the hypertension which follows constriction of one main renal artery is also followed by prompt return of the blood pressure to normal. It is interesting that Houssay, on the basis of transplantation of "ischemic kidneys," also concluded that the ischemic kidney secretes substances that cause permanent arterial hypertension.

Goldblatt [67] has also carried out various experiments on the effect of partial and complete adrenalectomy, with and without supportive and substitution therapy, which have indicated that the adrenal cortex, but not the medulla, may play a significant role in this type of hypertension. The manner in which the adrenal cortex acts in this regard is as yet

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Experimental Hypertension: III. The Production of Persistent Hypertension in Monkeys (Macaque) by Renal Ischemia, ibid. **65**:671, 1937. Goldblatt, H., and Wartman, W. B.: Studies on Experimental Hypertension: VI. The Effect of Section of Anterior Spinal Nerve Roots on Experimental Hypertension Due to Renal Ischemia, ibid. **66**:527, 1937. Freeman, N. E., and Page, I. H.: Hypertension Produced by Constriction of the Renal Artery in Sympathectomized Dogs, Am. Heart J. **14**:405, 1937. Dicker, E.: Recherches sur la pathogénie de l'hypertension: II. Une lésion rénale peut déterminer une élévation de la pression sanguine, Acta med. Scandinav. **93**:265, 1937.

66. Blalock, A., and Levy, S. E.: Studies on the Etiology of Renal Hypertension, Ann. Surg. **106**:826, 1937. Glenn, F.; Child, C. G., and Heuer, G. J.: Production of Hypertension by Constricting the Artery of a Single Transplanted Kidney: Experimental Investigation, ibid. **106**:848, 1937.

67. Goldblatt, H.: Studies on Experimental Hypertension: V. The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, Ann. Int. Med. **11**:69, 1937.

unknown; it may prepare the arteriolar musculature for the action of the hypothetic renal substance, or the reverse may be the case.

Page and Sweet [68] produced hypertension in dogs by means of Goldblatt's clamp and then removed the hypophysis. This reduced the arterial pressure to levels slightly above normal. If then, the constriction of the renal arteries was increased, a transient rise in pressure resulted; a rise in pressure also resulted if the dogs were fed thyroid. It was concluded that the effect of hypophysectomy on hypertensive dogs is indirect and probably associated with a lack of secretion from the adrenal and thyroid glands.

Wollheim [69] has found a depressor substance in the urine of normal men and horses which differs from other depressor substances previously described. It is absent or present only in small amounts in the urine of patients with essential hypertension or with hypertension due to renal disease.

Two excellent papers [70] have appeared on hypertension associated with benign chromaffin cell tumors. A fairly definite clinical picture is usually observable in these cases.

Longcope [71] has described his studies of 22 cases of chronic bilateral pyelonephritis. The clinical features of this disease, during its various stages, have been presented in some detail. Arterial hypertension was present in 10 of 15 patients who were observed during the terminal stages of the disease. The hypertension was not associated with pronounced or extensive arteriosclerosis in 9 fatal cases in which autopsy was performed. It was concluded that the explanation for the hypertension of pyelonephritis, occurring particularly during the latter stages of renal contraction, is not clear.

Butler [72] has reported his observations on children with chronic pyelonephritis and arterial hypertension. The blood pressure of 1 of the patients with unilateral pyelonephritis and hypertension returned to normal after removal of the infected kidney.

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68. Page, I. H., and Sweet, J. E.: The Effect of Hypophysectomy on Arterial Blood Pressure of Dogs with Experimental Hypertension, Am. J. Physiol. **120**:238, 1937.

69. Wollheim, E.: Eine neue körpereigene blutdrucksenkende Substanz und ihre Bedeutung für die essentielle Hypertonie, Acta med. Scandinav. **9**:1, 1937.

70. Howard, J. E., and Barker, W. H.: Paroxysmal Hypertension and Other Clinical Manifestations Associated with Benign Chromaffin Cell Tumors (Phaeochromocytomata), Bull. Johns Hopkins Hosp. **61**:371, 1937. Edward, D. G. F.: Phaeochromocytomata and Hypertension, with Details of a Case, J. Path. & Bact. **45**:391, 1937.

71. Longcope, W. T.: Chronic Bilateral Pyelonephritis: Its Origin and Its Association with Hypertension, Ann. Int. Med. **11**:149, 1937.

72. Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, J. Clin. Investigation **16**:889, 1937.

Liston [73] has reported interesting observations on 15 patients with food allergy in whom the ingestion of the offending foods caused a rise in blood pressure. Cure is effected simply by dietary regulation.

Shattuck [74] has measured the blood pressure of over 400 pure Indian and Spanish-Indian natives of Guatemala. The systolic pressure averaged about 10 mm. lower than that of North Americans living in the United States. Careful consideration of many factors suggested that the factors responsible for the lower systolic pressure of Guatemalans are racial characteristics, the slow tempo of life and a possibly deficient diet. The diastolic pressure of Guatemalans is nearer the standard for Americans in the United States than is the systolic pressure.

Hines [75] has considered the hereditary factor in essential hypertension. He found that a family history of hypertensive cardiovascular disease is five times as frequent among persons who have hypertension or who are hyperreactors to a standard stimulus test (cold pressor test) as it is among persons who react normally to the test. In the study of twins and family groups he found that the type of reaction of the blood pressure to the test followed an inherited pattern. Because hyperreactors were not found who did not have at least one parent who had hypertension or was a hyperreactor, he concluded that it is probable that the trait is inherited as a dominant characteristic and that the hereditary factor plays an important role in the development of essential hypertension.

Signs and Symptoms.—Two papers [76] have appeared on the electrocardiogram with a chest lead in cases of arterial hypertension. The various abnormalities were described, and it was concluded that chest leads are often of value.

Holden [77] found no evidence of a relation between blood pressure and cholesterol saturation of the plasma in a series which included patients with malignant hypertension, benign hypertension and chronic hemorrhagic nephritis. The plasma in all cases was approximately saturated with regard to free cholesterol, and the suggestion that supersaturation may exist was not substantiated.

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73. Liston, O.: Hypertension Caused by Food Allergy, J. Missouri M. A. **34**:199, 1937.

74. Shattuck, G. C.: The Possible Significance of Low Blood Pressures Observed in Guatemalans and in Yucatecans, Am. J. Trop. Med. **17**:513, 1937.

75. Hines, E. A.: The Hereditary Factor in Essential Hypertension, Ann. Int. Med. **11**:593, 1937.

76. van Nieuwenhuizen, C. I. C., and Hartog, H. A. T.: The Electrocardiogram in Hypertension, with Especial Reference to Lead IV, Am. Heart J. **13**:308, 1937. Roth, I. R.: Chest Lead Tracings in Arterial Hypertension with Cardiac Enlargement, ibid. **14**:155, 1937.

77. Holden, R. F., Jr.: Plasma Cholesterol Saturation in Patients with Hypertension, with a Note on Preparation of Glass Filters for Micro-Filtration of Cholesterol Digitonide, J. Clin. Investigation **16**:763, 1937.

Apperly and Cary [78] have shown that the increased chloride content of the blood of patients with arterial hypertension is wholly confined to the red blood cells.

Treatment.—The results of various operative procedures used in the treatment of arterial hypertension are, on the whole, not encouraging.

Page and Heuer [79] have found that resection of splanchnic nerves, with interruption of the thoracic sympathetic chain, resulted in only a temporary fall of blood pressure in 9 cases. Subjective improvement occurred in 6, but in 3 of these the improvement lasted only a year. Renal efficiency was unaffected by the procedure. The same authors [80] reported their results in the treatment of 17 hypertensive patients by section of the anterior roots of the sixth dorsal to the second lumbar spinal nerves. Six patients had benign and 5 had malignant hypertension; the remaining 6 were young women with signs and symptoms of the "hypertensive diencephalic syndrome." Varying degrees of improvement occurred in all patients save 2 of the 5 with malignant hypertension. The favorable responses included a marked prolonged lowering of the arterial pressure; the remission of such symptoms as headache, pressure in the head and easy fatigability, and marked improvement in the disposition. There was a definite tendency for a slow rise in pressure to occur over a period of two and one-half years in most but not all the patients. Renal efficiency remained unchanged, despite the partial denervation of the kidneys which resulted from the operation or from the fall in blood pressure.

Freyberg and Peet [81] have presented a report of interesting effects of splanchnicectomy on changes in the blood pressure and their relation to renal function. It is evident from their data that this procedure performed on patients with primary hypertension and normal renal function does not harm the kidneys or interfere with their functional efficiency. What is more important is that when hypertension is greatly relieved by splanchnicectomy, renal function that has previously been impaired improves and may even return to normal. This improvement has been declared both by an increase in concentrating ability and by an increase in urea clearance. It was concluded that the impairment of

78. Apperly, F. L., and Cary, M. K.: Arterial Hypertension: The Site and Significance of the High Chloride Content of the Blood, Am. J. M. Sc. **194**:352, 1937.

79. Page, I. H., and Heuer, G. J.: The Effect of Splanchnic Nerve Resection on Patients Suffering from Hypertension, Am. J. M. Sc. **193**:820, 1937.

80. Page, I. H., and Heuer, G. J.: Treatment of Essential and Malignant Hypertension by Section of Anterior Nerve Roots, Arch. Int. Med. **59**:245 (Feb.) 1937.

81. Freyberg, R. H., and Peet, M. M.: The Effect on the Kidney of Bilateral Splanchnicectomy in Patients with Hypertension, J. Clin. Investigation **16**:49, 1937.

renal function is caused by vascular constriction and that if this constriction is relieved by splanchnicectomy, renal activity is benefited.

Other papers [82] have also appeared dealing with various operative procedures or their complications in the treatment of hypertension. From a review of all these studies it seems safe to conclude that section of the anterior nerve roots has given the best therapeutic results, although it is a serious operation, that partial removal of the normal adrenal glands is unsatisfactory and that improvement following the section of various nerves may be due to improved circulation through the kidneys as well as, or rather than, to simple denervation of a large vascular area. We believe, however, that there have not been adequate control studies; convalescence after any operation of course has a salutary effect on patients with hypertension.

Reports on various medical methods of treating hypertension have appeared, including salt restriction,[83] thiocyanate therapy,[84] the "class method" [85] and the effect of deep breathing.[86] All have indicated at least some degree of success.

HEART DISEASE DUE TO CORONARY ARTERIOSCLEROSIS

Glendy, Levine and White [87] have made an interesting study of coronary disease in youth, including a comparison of 100 patients with this disease under 40 years of age with 300 healthy persons past 80 years of age. Of the 100 young patients, the diagnosis of coronary

82. Hermann, H., and Sabadini, L.: La résection des nerfs splanchniques est-elle légitime comme traitement de l'hypertension artérielle essentielle permanente? Presse méd. **45**:41, 1937. Allen, E. V., and Adson, A. W.: The Physiological Effects of Extensive Sympathectomy for Essential Hypertension, Am. Heart J. **14**:415, 1937. Craig, W. M., and Adson, A. W.: Rationale of Surgical Treatment of Hypertension, S. Clin. North America **17**:1063, 1937. Donzelot, E., and Ménétrel, B.: La surrénalectomie dans les hypertensions arterielles, Arch. d. mal. du cœur **30**:553, 1937. Lowenstein, W., and Weissmann, A.: Zur Frage der Nierenstielentnervung bei der Hypertension, Wien. med. Wchnschr. **87**:675, 1937. Leriche, R.: Des douleurs provoquées par l'excitation du bout central des grands splanchniques (douleurs cardiaques, douleurs pulmonaires) au cours des splanchnicotomies, Presse méd. **45**:971, 1937.

83. Steffen, H. L.: Zur Behandlung Kranker mit erhöhtem Blutdruck durch Kochsalzentzug, Deutsche med. Wchnschr. **63**:90, 1937.

84. Griffith, J. Q., Jr., and Lindauer, M. A.: Thiocyanate Therapy in Hypertension, Including a New Method for Determining Blood Thiocyanates, Am. Heart J. **14**:710, 1937.

85. Buck, R. W.: The Class Method in the Treatment of Essential Hypertension, Ann. Int. Med. **11**:514, 1937.

86. Tirala, L. G.: Die Wirkung des Tiefatmens auf den Blutdruck, Deutsche med. Wchnschr. **63**:92, 1937.

87. Glendy, R. E.; Levine, S. A., and White, P. D.: Coronary Disease in Youth: Comparison of One Hundred Patients Under Forty with Three Hundred Persons Past Eighty, J. A. M. A. **109**:1775 (Nov. 27) 1937.

thrombosis was established clinically in 78, 70 had angina pectoris and 49 had both conditions. One patient had neither angina pectoris nor clinically evident coronary thrombosis but showed electrocardiographic evidence of serious coronary disease. The ratio of men to women was 24:1. Hypertension was found to be less common than in persons of all ages with coronary disease but was present in 3 of the 4 women in the group. The size of the heart was normal in over half the young patients, and, in general, the electrocardiographic observations were much the same as those for older patients. The prognosis of coronary disease in patients under 40 is considerably better than that in older patients, but much the same uncertainty exists.

Their summary of the prominent differences as to mode of life between the 100 young patients with coronary disease and the 300 healthy persons over 80 years of age was as follows:

> Relatively far more (90 per cent) of the old folks than of the young group with coronary disease were of British stock, but here selection and other factors, such as time of immigration, may well enter. There were no persons of Jewish extraction in the older group, whereas 39 per cent of the young group were Jewish. Long-lived ancestors were more common to the aged group. However, it is of interest that the fathers of the younger group who died outlived the mothers by an average of five years. This relationship is usually reversed by several years. The majority of the old group have resided in small towns, villages or the country, in contrast to the young group, whose residence has been almost wholly urban. The younger group consisted largely of business or professional men. Among the old folks the occupations requiring physical activity were more common. A large number of the old group had exercised considerably to well beyond middle life. The young group were for the most part sedentary in habit and exercised very little.
>
> The older group claimed to have eaten more moderately and perhaps more sparingly of such cholesterol-containing foods as milk and eggs. Tobacco was used in greater quantity and by a greater number in the young group, the incidence of smokers being 93 per cent, which exceeds even the high incidence in the general population. The use of alcohol differs less widely for the two groups. There were slightly more total abstainers in the old group and few heavy drinkers in either group. With rare exceptions a history of serious infections (e. g., smallpox, typhoid fever and malaria) was much more common in the older group. A greater proportion of the older group were exemplary in their sleeping habits, and fewer of them were constipated. Nearly 70 per cent of the young group were robust in build or distinctly fat, whereas 83 per cent of the old folks were of average build or had been thin and lean for most of their lives. Nervous sensitivity and strain were frequently encountered in the young group but practically negligible in the older group.

Davis and Blumgart [88] studied the relation of cardiac hypertrophy to coronary arteriosclerosis and congestive heart failure. They found

88. Davis, D., and Blumgart, H. L.: Cardiac Hypertrophy: Its Relation to Coronary Arteriosclerosis and Congestive Heart Failure, Ann. Int. Med. **11**:1024, 1937.

that in patients with the lesser degrees of coronary arteriosclerosis the heart undergoes little or no hypertrophy, while with more serious involvement a slight or moderate degree of hypertrophy is seen. When, in addition to coronary arteriosclerosis, the factor of congestive failure is added, the resulting cardiac hypertrophy is usually marked; the degree of cardiac hypertrophy seemed generally proportional to the severity and duration of congestive failure. They concluded that these results support the "injury theory" of the causation of cardiac hypertrophy rather than the widely held "work hypertrophy theory."

Snellen and Nauta [89] have emphasized that in the routine examination of the thorax roentgenographically it is often possible to detect calcification of the coronary arteries when this is present. It may well be that this method of diagnosing coronary arteriosclerosis will find wider application than it has thus far.

Gross and his associates [90] found that ligation of the coronary sinus in dogs was followed by considerable dilatation and widening of existing vascular channels on the surface of the heart and a conspicuous increase in the extent of the vascular bed. Subsequent occlusion of the left descending coronary branch was not followed by infarction in the majority of instances. It was further shown that partial occlusion of the coronary sinus, which is associated with a low operative mortality, appears to lower the mortality rate following sudden occlusion of the left anterior descending branch and to diminish the extent of the infarction. The possibility of applying this procedure to man was mentioned.

Blumgart and his co-workers [91] have reported their experiments designed to learn whether temporary interruption of the blood supply to a portion of the heart results in persistent electrocardiographic or anatomic changes. Electrocardiographic changes were found to persist during the entire postoperative period (one to nine days) in all animals in which occlusion was maintained for from fifteen to forty minutes. When the period of occlusion was ten minutes or less, the electrocardiographic changes persisted in only 1 instance. Postmortem examinations did not reveal gross or histologic evidence of cardiac infarction in any instance. The clinical counterpart of these tests is suggested by

89. Snellen, H. A., and Nauta, J. H.: Zur Röntgendiagnostik der Koronarverkalkungen, Fortschr. a. d. Geb. d. Röntgenstrahlen **56**:277, 1937.

90. Gross, L.; Blum, L., and Silverman, G.: Experimental Attempts to Increase the Blood Supply to the Dog's Heart by Means of Coronary Sinus Occlusion, J. Exper. Med. **65**:91, 1937.

91. Blumgart, H. L.; Hoff, H. E.; Landowne, M., and Schlesinger, M. J.: Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries in Producing Persistent Electrocardiographic Changes, Am. J. M. Sc. **194**:493, 1937.

those patients with angina pectoris who show persistent electrocardiographic abnormalities and for whom postmortem examination reveals neither coronary occlusion nor myocardial infarction.

Whitten [92] has stated that the use of a midaxillary or lateral thoracic lead of the electrocardiogram in some cases appears to show earlier and to a more marked degree than the limb leads the electrocardiographic changes characteristic of infarction of the T_1 type. In not a single case did inversion of T_1 or T_2 or significant depression or elevation of RS-T_1 or RS-T_2 occur in the midaxillary lead unless there was definite reason to suspect cardiac damage; furthermore, in every instance of inversion of T_1 in the limb lead this degree of inversion was equaled or exceeded in the midaxillary lead. In the T_3 type of infarction, whether or not it is combined with the T_1 type, the limb lead provides a better record than the midaxillary lead.

Master, Dack and Jaffe,[93] and Kerr,[94] among others, have discussed various types of cardiac arrhythmia observed in cases of coronary thrombosis. Of the various arrhythmias, heart block alone appears to be associated with a specific anatomic lesion in the heart, namely, infarction of the posterior wall due to occlusion of the right coronary artery. Arrhythmia provoked by acute arterial occlusion is often ephemeral and remits spontaneously.

Wolferth [95] has written an excellent article which adequately expresses the present day clinical concepts of acute coronary occlusion. Master, Dack and Jaffe [96] have contributed an important study on factors and events associated with the onset of coronary thrombosis. The reasonable conclusion was reached that no known specific factor precipitates this thrombosis. Feil,[97] and Sampson and Eliaser [98] have emphasized the importance and have described the characteristics of attacks of precordial pain which may represent a precursory phenomenon of characteristic acute coronary occlusion.

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92. Whitten, M. B.: Midaxillary Leads of the Electrocardiogram in Myocardial Infarction, Am. Heart J. **13**:701, 1937.

93. Master, A. M.; Dack, S., and Jaffe, H. L.: Disturbances of Rate and Rhythm in Acute Coronary Artery Thrombosis, Ann. Int. Med. **11**:735, 1937.

94. Kerr, J. D. O.: Heart Block in Coronary Thrombosis, Lancet **2**:1066, 1937.

95. Wolferth, C. C.: Present Concepts of Acute Coronary Occlusion, J. A. M. A. **109**:1769 (Nov. 27) 1937.

96. Master, A. M.; Dack, S., and Jaffe, H. L.: Factors and Events Associated with Onset of Coronary Artery Thrombosis, J. A. M. A. **109**:546 (Aug. 21) 1937.

97. Feil, H.: Preliminary Pain in Coronary Thrombosis, Am. J. M. Sc. **193**:42, 1937.

98. Sampson, J. J., and Eliaser, M.: The Diagnosis of Impending Acute Coronary Artery Occlusion, Am. Heart J. **13**:675, 1937.

Blumer,[99] and Gravier and his associates [100] have commented on the importance of embolism as a complication of cardiac infarction. Intracardiac thrombi are present in about 50 per cent of the cases, and clinically recognizable embolic phenomena occur in about 14 per cent. Embolism is most likely to occur during the first ten days following cardiac infarction. Protracted rest and the avoidance of the use of digitalis, unless specially indicated, are important.

Palmer [101] studied the prognosis, size of the heart and changes in the blood pressure following coronary thrombosis. He found that hypertensive patients have a somewhat more favorable outlook than nonhypertensive patients but that changes in the blood pressure and the height of the blood pressure after recovery from coronary thrombosis are of little significance. Cardiac enlargement is a most important factor in causing restriction of activity, and the prognosis for the patient with an enlarged heart and with congestive failure is slightly less favorable. He concluded that hypertension is by far the most important factor causing cardiac enlargement after coronary thrombosis. This is not in full agreement with the previously mentioned conclusion of Davis and Blumgart.[88]

Angina Pectoris.—There have been a number of worth while articles on various aspects of coronary heart disease and angina pectoris,[102] but they will not be reviewed here.

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99. Blumer, G.: The Importance of Embolism as a Complication of Cardiac Infarction, Ann. Int. Med. **11**:499, 1937.

100. Gravier, L.; Tourniaire, A., and Bourret, M.: Les embolies pulmonaires au cours de l'infarctus du myocarde, Lyon méd. **160**:357, 1937.

101. Palmer, J. H.: The Prognosis Following Recovery from Coronary Thrombosis, with Special Reference to the Influence of Hypertension and Cardiac Enlargement, Quart. J. Med. **6**:49, 1937; The Size of the Heart After Coronary Thrombosis, Canad. M. A. J. **36**:387, 1937; The Blood Pressure in the Years Following Recovery from Coronary Thrombosis, Lancet **1**:741, 1937.

102. Bourne, G.; Scott, R. B., and Wittkower, E.: The Psychological Factor in Cardiac Pain, Lancet **2**:609, 1937. Wittkower, E.: The Psychological Factor in Cardiac Pain, ibid. **2**:665, 1937. Bourne, G.: Angina Innocens: Clinical Study, Brit. M. J. **1**:695, 1937. White, P. D.: The Criteria for the Diagnosis of Coronary Disease, New England J. Med. **217**:783, 1937. Riseman, J. E. F., and Brown, M. G.: An Analysis of the Diagnostic Criteria of Angina Pectoris, Am. Heart J. **14**:331, 1937. Stalker, H.: Angina Pectoris and Pernicious Anemia (Old Terminology): A Résumé of the Literature, with a Case Report, Ann. Int. Med. **10**:1172, 1937. Burnett, C. T.: Pain and Pain Equivalents in Heart Disease, ibid. **10**:1156, 1937. Boas, E. P., and Levy, H.: Extracardiac Determinants of the Site and Radiation of Pain in Angina Pectoris, with Special Reference to Shoulder Pain, Am. Heart J. **14**:540, 1937. Seymour, W. B., and Liebow, A. A.: "Abdominal Intermittent Claudication" and Narrowing of the Celiac and Mesenteric Arteries, Ann. Int. Med. **10**:1033, 1937.

The outstanding recent development in the treatment of angina pectoris concerns the possibility of substantially increasing the collateral coronary circulation by surgical means.[103]

Beck's operation consists principally of grafting vascularized fat and muscle on to the heart and sometimes placing powdered beef bone on the surface of the heart to produce a low grade inflammatory reaction. Thus far 25 patients with advanced coronary disease and angina pectoris have been operated on. Of these, 16 are living and 9 are dead; 8 of the deaths occurred within one week of the operation. Thirteen patients have been observed for five months or longer after the operation; 3 have improved greatly, 9 moderately and 1 slightly. The beneficial effect of the operation may be explained by an actual increase in arterial blood flow to the myocardium and a redistribution of blood that passes through the coronary arteries. The latter is brought about by opening up intercoronary communications by means of trauma, grafts and powdered bone placed on the surface of the heart. Beck concluded that the procedure is scientifically sound and that the results so far are encouraging. Although recognizing the interest and importance of this operative treatment, we wish to emphasize the natural tendency of spontaneous adjustment of the coronary circulation in many instances with no especial treatment at all.

O'Shaughnessy[104] has performed cardio-omentopexy on 5 patients with coronary heart disease. This operation consists in opening the chest by making an incision along the fifth intercostal space, incising the diaphragm and bringing a suitable portion of omentum into the thoracic cavity. The pericardium is incised, and the omentum is attached to the surface of the heart and to the edges of the pericardium. Six patients have submitted to this operation; 4 are much improved and 2 have died. The 2 deaths were not the result of operation but due to hemorrhage from a duodenal ulcer in one instance and uremia in the other. The results are encouraging indeed.

Love,[105] and Willius and Dry[106] have reported their results of the treatment of angina pectoris with trichlorethylene. Although the results were disappointing, it was suggested that this drug warrants a trial when the usual therapeutic agents fail to give relief.

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103. Feil, H., and Beck, C. S.: The Treatment of Coronary Sclerosis and Angina Pectoris by Producing a New Blood Supply to the Heart, J. A. M. A. **109**:1781 (Nov. 27) 1937. Mautz, F. R., and Beck, C. S.: The Augmentation of Collateral Coronary Circulation by Operation, J. Thoracic Surg. **7**:113, 1937.

104. O'Shaughnessy, L.: Surgical Treatment of Cardiac Ischaemia, Lancet **1**:185, 1937.

105. Love, W. S., Jr.: The Effectiveness of Trichlorethylene in Preventing Attacks of Angina Pectoris, Ann. Int. Med. **10**:1187, 1937.

106. Willius, F. A., and Dry, T. J.: Results from Trichlorethylene Inhalations in the Anginal Syndrome of Coronary Sclerosis, Am. Heart J. **14**:659, 1937.

Gold and his associates [107] studied the effect of theobromine and aminophylline on cardiac pain in a group of 100 patients with angina pectoris. Great care was taken to insure valid results, including the use of the so-called blind test and the alternate use of placebos and the xanthines. Their results showed that patients with cardiac pain are unable to distinguish between the effects of theobromine or aminophylline and those of a placebo. It was concluded, therefore, that the xanthines exert no specific action which is useful in the routine treatment of cardiac pain. Laubry, Soulie and Laubry [108] similarly concluded that theophylline with ethylenediamine is of small value in the treatment of chronic coronary disorders.

Brown and Riseman,[109] however, concluded that definite improvement occurs in some patients with angina pectoris after the use of xanthines. By therapeutic test it was shown that the optimum dosage is usually the maximum amount that can be given without causing severe gastric distress and that the sodium acetate derivatives of theophylline and theobromine are the most effective preparations; the latter is much less expensive.

In connection with the foregoing observations concerning the effect of aminophylline in coronary disease, it is our clinical impression that patients who have advanced beyond the simple stage of angina pectoris to the state of myocardial weakness are most benefited by the drug. The benefit from the drug in such cases may be due in part to its diuretic effect and its stimulation of respiration.

MISCELLANEOUS CARDIAC DISORDERS

The Heart in Nutritional Deficiency States.—For many years it has been known that cardiac enlargement and congestive failure may occur in beriberi. Recently Wenckebach and his associate Aalsmeer have greatly extended the knowledge of a group of disturbances of cardiac muscle in deficiency diseases, especially beriberi. During the past year several articles have appeared on this subject, the most notable being the contributions of Weiss and Wilkins.[110]

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107. Gold, H.; Kwit, N. T., and Otto, H.: The Xanthines (Theobromine and Aminophylline) in the Treatment of Cardiac Pain, J. A. M. A. **108**:2173 (June 26) 1937.

108. Laubry, C.; Soulie, P., and Laubry, P.: Action de la théophylline éthylène-diamine sur la circulation coronarienne, Arch. d. mal. du cœur **30**:256, 1937.

109. Brown, M. G., and Riseman, J. E. F.: The Comparative Value of Purine Derivatives in the Treatment of Angina Pectoris, J. A. M. A. **109**:256 (July 24) 1937.

110. Weiss, S., and Wilkins, R. W.: The Nature of the Cardiovascular Disturbances in Nutritional Deficiency States (Beriberi), Ann. Int. Med. **11**:104, 1937; Disturbances of the Cardiovascular System in Nutritional Deficiency, J. A. M. A.

These last named authors have shown that dysfunction of the cardiovascular system resulting from avitaminosis may occur in the United States and that in some respects the clinical picture resembles that of the classic "beriberi heart" observed in the Orient. Vitamin B deficiency plays the primary role in the precipitation of the disease. In the majority of cases there is moderate dilatation of the right ventricle, although the weight of the heart is not increased. The histologic changes in the myocardium include "hydropic" degeneration of the muscle and conductive fibers and increase in the intercellular substances, but the water content is unaltered. The signs and symptoms of the disorder do not form a rigid clinical syndrome; failure of the right or of the left ventricle, peripheral circulatory collapse and shock, singly or in combination, have been observed. The venous pressure is usually high, the arterial pressures normal and the blood velocity increased. The electrocardiograms in the great majority of cases reveal some abnormality. Digitalis is of no value, but vitamin B is a specific cure. These patients are seen mostly in the wards for alcoholic addicts of the large city hospitals and rarely in the other wards or in private practice.

The Heart After Diphtheria.—Thompson, Golden and White [111] carefully studied 100 persons who had had severe or moderately severe diphtheria fifteen to twenty years previously. No clear instance of auriculoventricular or intraventricular block was found, and it was concluded that while there are acceptable cases of the development of disturbed conduction during the course of diphtheria and that in rare cases the disturbance persists permanently, there is as yet no proof that it may develop several years after the illness.

Blastomycosis of the Heart.—Baker and Brian [112] have described 2 cases of generalized blastomycosis with cardiac involvement. No characteristic signs or symptoms of heart disease were discovered.

Cardiac Changes in Anemia Due to Hookworm.—Porter [113] has described certain physiologic adjustments to chronic anemia due to hookworm. Of particular interest was the cardiac enlargement which was found in every case studied. The data indicate that the change in

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109:786 (Sept. 4) 1937. Porter, W. B., and Higginbotham, U.: The Heart in Endemic Pellagra, South. M. J. **30**:1, 1937. Hashimoto, H.: Acute Pernicious Form of Beriberi and Its Treatment by Intravenous Administration of Vitamin B, with Especial Reference to Electrocardiographic Changes, Am. Heart J. **13**:580, 1937.

111. Thompson, W. P.; Golden, S. E., and White, P. D.: The Heart Fifteen to Twenty Years After Severe Diphtheria, Am. Heart J. **13**:534, 1937.

112. Baker, R. D., and Brian, E. W.: Blastomycosis of the Heart: Report of Two Cases, Am. J. Path. **13**:139, 1937.

113. Porter, W. B.: Heart Changes and Physiologic Adjustment in Hookworm Anemia, Am. Heart J. **13**:550, 1937.

cardiac size was in a few cases due to reducible dilatation, in others to dilatation and hypertrophy and in still others to definite hypertrophy unassociated with reducible dilatation. The primary cardiac dilatation may be classed as a physiologic adjustment mechanism which disappears when the anemia is relieved; yet if those factors which have necessitated the dilatation continue, there occurs hypertrophy of the myocardium which is not reducible and which is definitely pathologic.

Arteriovenous Fistula.—Porter and Baker [114] have studied in 4 patients the significance of cardiac enlargement caused by arteriovenous fistula. It was concluded that the increase in cardiac size is primarily an adjustment dilatation and that there is little hypertrophy present. This dilatation is not the result of decreased myocardial nutrition.

Cardiac Neurosis.—White and Glendy [115] have emphasized the growing importance of cardiac neurosis occasioned by the large amount of publicity accorded to heart disease. The early recognition and proper treatment in such cases may spare these subjects much time, money and suffering.

Trauma and Heart Disease.—White and Glendy [116] have written a comprehensive but concise report on trauma and heart disease. The general principles of the subject have been discussed, followed by consideration of etiologic relations, structural changes and functional derangements. Illustrative cases have been presented.

Aviation and Heart Disease. — Graybiel and his associates [117] described some effects of asphyxiation in patients with cardiac disease. Thirteen patients with heart disease and a like number of normal persons were subjected to an oxygen tension corresponding to an elevation of 14,500 feet (4.5 kilometers). The most striking feature of the test was the absence of complaint on the part of any subject, despite the fact that 3 of the patients fainted and 4 others exhibited signs of circulatory embarrassment. It was concluded that many patients with cardiac disease are endangered at high altitudes and that the untoward effects observed may be due to the general unfitness which is so often associated with heart disease or due more directly to embarrassment of the heart itself.

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114. Porter, W. B., and Baker, J. P.: The Significance of Cardiac Enlargement Caused by Arteriovenous Fistula, Ann. Int. Med. **11**:370, 1937.

115. White, P. D., and Glendy, R. E.: The Growing Importance of Cardiac Neurosis, Ann. Int. Med. **10**:1624, 1937.

116. White, P. D., and Glendy, R. E., in Brahdy, L., and Kahn, S.: Trauma and Disease, Philadelphia, Lea & Febiger, 1937, p. 24.

117. Graybiel, A.; Missiuro, W.; Dill, D. B., and Edwards, H. T.: Experimentally Induced Asphyxiation in Cardiac Patients with Special Reference to Certain Hazards in Air Travel and to the Use of Asphyxiation as a Cardiac Functional Test, J. Aviation Med. **8**:3, 1937.

HEART FAILURE AND ITS TREATMENT

There have been a number of interesting articles [118] bearing on the general subject of heart failure which cannot be reviewed because of considerations of space. Little advance has been made in regard to the treatment of congestive failure, although a few good reviews have appeared. Two volumes giving good résumés of the subject of congestive failure appeared in 1937, a small one by East [119] and the other, a large volume by Fishberg,[120] which treated the various aspects of the subject in considerable detail.

Wood and his associate [121] have used the term trepopnea to describe a phenomenon noted in certain cases of cardiac disease, namely, that the patient is comfortable in one recumbent position and uncomfortable in another recumbent position. This is probably due to a shift in position of the heart under the influence of gravity, which causes pressure

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118. Greene, J. A.; Paul, W. D., and Feller, A. E.: The Action of Theophylline with Ethylenediamine on Intrathecal and Venous Pressures in Cardiac Failure and on Bronchial Obstruction in Cardiac Failure and in Bronchial Asthma, J. A. M. A. **109**:1712 (Nov. 20) 1937. Marais, O. A. S., and McMichael, J.: Theophylline-Ethylenediamine in Cheyne-Stokes Respiration, Lancet **2**:437, 1937. Cowan, J. H.: Observations on Coramine, Am. J. M. Sc. **193**:673, 1937. Heim de Balsac, R.: La théophylline éthylène-diamine (aminophylline) dans la pratique cardio-vasculaire, Paris méd. **2**:423, 1937. Thomson, W. A. R.: The Organic Mercurial Diuretics in the Treatment of Cardiac Oedema, Quart. J. Med. **6**:321, 1937. Herrmann, G., and Decherd, G. M., Jr.: Further Studies on the Mechanism of Diuresis, with Especial Reference to the Action of Some Newer Diuretics, J. Lab. & Clin. Med. **22**:767, 1937. Smith, F. M.: Treatment of Left Ventricular Failure, J. A. M. A. **109**:646 (Aug. 28) 1937. Stroud, W. D., and Vander Veer, J. B.: A Six Year Study of the Clinical Efficacy of Various Digitalis Preparations, ibid. **109**:1808 (Nov. 27) 1937. Moldavsky, L. F., and Visscher, M. B.: The Energy Liberation at Constant Diastolic Fibre Length in the Tortoise Heart, with Particular Reference to the Effect of the Emptying Pressure, J. Physiol. **91**:23, 1937. Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: III. Changes in Blood Volume, Venous Pressure and Blood Velocity Rate in Chronic Congestive Heart Failure, J. Clin. Investigation **16**:851, 1937. Thelen, A.: Die venöse Blutstauung im Herzmuskel, Virchows Arch. f. path. Anat. **300**:243, 1937. Farber, S.: Studies on Pulmonary Edema: I. The Consequences of Bilateral Cervical Vagotomy in the Rabbit; II. The Pathogenesis of Neuropathic Pulmonary Edema, J. Exper. Med. **66**:397, 1937. Burns, W., and Cruickshank, E. W. H.: Changes in Creatine, Phosphagen and Adenylpyrophosphate in Relation to Gaseous Metabolism of the Heart, J. Physiol. **91**:314, 1937. Lewis, N. D. C.: Psychic Phenomena in Association with Cardiac Failure, Arch. Neurol. & Psychiat. **37**:782 (April) 1937.

119. East, T.: Failure of the Heart and Circulation, London, John Bale, Sons & Curnow, Ltd., 1937.

120. Fishberg, A. M.: Heart Failure, Philadelphia, Lea & Febiger, 1937.

121. Wood, F. C., and Wolferth, C. C.: The Tolerance of Certain Cardiac Patients for Various Recumbent Positions (Trepopnea), Am. J. M. Sc. **193**:354, 1937.

on certain mediastinal structures. The symptoms which force the patient to change position are usually dyspnea, precordial pain and cough. Most patients with trepopnea prefer lying on the right side and dislike lying on the left, but others have different preferences. In certain cases trepopnea is an etiologic factor in the production of paroxysmal nocturnal dyspnea.

Schnitker and Levine [122] have sought to explain the postdiuretic symptoms occasionally observed in digitalized patients. The transportation of a large amount of fluid from the body cavities and interstitial spaces through the body to the kidneys would expose the cardiovascular and nervous systems to the effect of any digitalis contained in this fluid. That such "redigitalization" is possible was shown by the discovery that body fluids from digitalized patients usually contained a significant amount of digitalis. It is conceivable that 0.5 Gm. or more of digitalis could be mobilized after marked diuresis—an amount which could provoke such symptoms as headache, giddiness, weakness, nausea and even vomiting. Further studies are necessary to substantiate the idea of digitalis intoxication with diuresis.

Macrez,[123] in an excellent article, has reviewed the subject of the use of opiates for patients with heart disease. Opiates have been out of favor several times in the past; the last time was shortly after Charcot died of acute pulmonary edema which was treated with morphine. At that time Huchard interdicted the use of morphine because of its supposedly depressing action on the heart and kidneys. Macrez, from the results of well authenticated animal and clinical investigations, has shown that opiates rarely have any untoward effect on the central nervous system, heart or kidneys but usually have a decidedly salutary effect. In regard to the dangers of habituation he has emphasized the fact that opiates are seldom needed over long periods by patients with cardiac disease save in terminal circumstances. A list of cardiovascular diseases in which opiates are indicated includes all those in which pain or dyspnea are prominent symptoms. The author concluded that there is scarcely a contraindication to their "lavish" use and that the risks are minimal.

The results [124] of total thyroidectomy in the treatment of heart disease are not gratifying. Apparently only a few patients with congestive failure are suitable for the operation. Patients with angina pectoris may often obtain symptomatic relief after total thyroidectomy, but a myxedematous state is not desirable and the operation carries considerable risk.

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122. Schnitker, M. A., and Levine, S. A.: Presence of Digitalis in the Body Fluids of Digitalized Patients, Arch. Int. Med. **60**:240 (Aug.) 1937.

123. Macrez, C.: La morphine chez les cardiaques, Paris méd. **2**:221, 1937.

124. Parsons, W. H., and Purks, W. K.: Total Thyroidectomy for Heart Disease, Ann. Surg. **105**:722, 1937. Claiborne, T. S., and Hurxthal, L.: Results of Total Thyroidectomy in Heart Disease, New England J. Med. **216**:411, 1937.

News and Comment

Reprints of General Reviews.—Requests have been received for annual reprints of the general reviews which since 1935 have been published in the ARCHIVES OF INTERNAL MEDICINE on allergy, diseases of metabolism and nutrition, the liver and biliary tract, diseases of the heart, blood, Bright's disease, infectious diseases, peripheral vascular diseases, gastroenterology, syphilis and neuropsychiatry. The type has been held, and if there is sufficient demand reprints of each year's reviews will be prepared.

Edward N. Gibbs Memorial Prize.—It is announced by the New York Academy of Medicine, 2 East One Hundred and Third Street, New York, that a sum of approximately $1,000 is available under the Edward N. Gibbs Memorial Prize toward original research in diseases of the kidney during 1938.

Candidates must be physicians who have been graduated at least three years and who are residents of the United States. They are requested to submit "evidence of research already performed and of facilities to prosecute research upon the causation, pathology and new methods of treatment of diseases of the kidney."

The award may be continued through not more than three years to any one person.

Applications with the required evidence should be addressed to the New York Academy of Medicine prior to June 1.

International Congress of Cosmobiology.—The first International Congress of Cosmobiology will be held on the Côte d'Azur, June 2 to 6, 1938, under the auspices of the Société médicale de climatologie et d'hygiène du littoral Méditerranéen, with the collaboration of the Association internationale pour l'étude des radiations solaires, terrestres et cosmiques. Professor d'Arsonval, of the Institut de France, is chairman of the radiologic division, and A. Lumière, correspondent of the Academy of Sciences and Medicine, is chairman of the biologic division.

The program will include: prehistory, protohistory and history of the knowledge of the action of the forces of the universe on terrestrial life; notions of astronomy and astrophysics, the solar corona and the periods of solar effervescence and their influence on crops; solar spectrum (ultraviolet and infra-red)—biologic, pathologic and therapeutic actions; other radiations emitted by the sun; undulatory or corpuscular rays called cosmic; high atmosphere and terrestrial magnetism; meteorology in its relations to morbid manifestations, on one hand, with atmospheric electricity and cosmic influences on the other; the constitution of microclimates and their utilization in medicine and botany; electric conductivity and ionization of the air—their eventual action on living beings; radioactivity of stone and soil—biologic, pathologic and therapeutic action; thermal and mineral waters.

Book Reviews

Klinische Elektrokardiographie mit einem Grundriss der Arrhythmien. By Dr. Wilhelm Dressler. Fourth edition. Price, 10.50 marks. Pp. 180, with 151 illustrations. Berlin: Urban & Schwarzenberg, 1937.

This is a handbook of electrocardiography for the practicing physician without special training in this field of medicine. Professor Rothberger in an introductory note recommends the book for its usefulness to this group of physicians, more of whom, he believes, should employ the electrocardiograph. The conservatism in the evaluation of evidence of cardiac damage is indicated by the fact that the author does not mention the doubtfully significant minor changes, by his clear definition of normal variations, by his correlation of the electrocardiographic findings with clinical symptoms and signs and by his emphasis on the uncertainty of the prognostic value in the individual case. This conservatism is desirable because it should help the practicing physician avoid the usual mistakes of those inexpert in this field.

The major part of the volume is concerned with the arrhythmias. Dressler recognizes the present predominant interest in the evidence of myocardial damage apart from the arrhythmias, but he believes that the detection of the presence and of the particular type of arrhythmia will always be an important function of the electrocardiogram. For each type of arrhythmia, in addition to the electrocardiographic findings the author presents a brief review of the pathologic physiology, symptoms, signs, diagnosis, prognosis and treatment. This clarifies and coordinates an otherwise puzzling subject.

The following are points of interest in regard to the electrocardiographic changes in cases of myocardial damage. Dressler rightly emphasizes the point that the general state of the myocardium is reflected chiefly in the RS-T interval and the T wave. He describes the type of electrocardiogram with hypertrophy of the left ventricle in which the RS-T segment in lead I is depressed and T wave inverted and states that this in itself is not evidence of myocardial damage in the usual sense. He believes that it may be caused partially by a disturbance in the excitatory pathway in the hypertrophied ventricle, thus having a mechanism somewhat similar to that of the electrocardiogram with oppositely directed QRS complexes and T waves seen in cases of defects of intraventricular conduction. He does not regard a Q_3 wave as significant unless Q_2 is also present. He believes that the precordial lead has definite limitations of usefulness in clinical diagnosis because it expresses changes chiefly in the myocardium directly underlying the electrode. He advises conservative evaluation of changes in the precordial lead, especially regarding the upright T wave. His statement that the Q_3, T_3 type of electrocardiogram, indicating infarct of the posterior wall, carries a better prognosis than that indicating anterior infarction is controverted by other careful studies of this question.

In discussing the evidence of chronic myocardial damage the author mentions changes in the T wave and the RS-T segment in leads I and II but does not mention the equally significant although less frequent change seen in the second and third leads with acute and chronic strain of the right ventricle. He says that the temporary depression of the RS-T interval in leads I and II with corresponding changes in the T wave seen during an attack of angina pectoris may become permanent. Under figure 130 he describes an example of this in a case of syphilitic aortitis in which there were attacks of substernal pain. Since this type of electrocardiogram is so frequently seen in cases of strain of the left ventricle of various types and without necessarily the presence of disease of the coronary arteries, it is doubtful whether this should be considered evidence in the case cited and in other cases mentioned of disease of the coronary arteries.

The Avitaminoses. The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases. By Walter H. Eddy, Ph.D., and Gilbert Dalldorf, M.D. Price, $4.50. Pp. 338, with 32 illustrations. Baltimore: Williams & Wilkins Company, 1937.

This book is described as a derivation from "The Vitamine Manual," which was written by the senior author fifteen years ago. It is divided into two parts. Part 1 considers the vitamins and the avitaminoses. It deals with the nature and functions of the important vitamins, together with the clinical aspects and anatomic manifestations of their deficiency. Part 2 is devoted to methods of assaying sources of vitamins, clinical tests of the deficiencies and a table of the vitamin values of foods.

The chapters on vitamin A bring together much new information. The two mechanisms of the production of ocular changes are clearly outlined, and the development of the widespread lesions of vitamin A deficiency are explained. The chapters on the subclinical forms of avitaminosis A, B and C are particularly important in that they emphasize the little known fact that mild deficiencies are prevalent and may produce only nonspecific symptoms and signs. Clinical indications of their presence may, in many instances, lead to verification by special procedures. The discussion of the pellagra problem is highly colored by the beliefs of the authors. However, the present status of the flavins is clarified. The section on pellagra and that on vitamin E demonstrate an important weakness found throughout the book. Controversial information is given without adequate discussion. Facts and observations of other investigators are often merely listed. Correlation and interpretation may be lacking where they are most needed by the physician, and elsewhere dogmatism is manifest regarding an equally controversial topic.

The last three chapters concern methods of vitamin bioassay, clinical tests and the vitamin values of foods. The descriptions of methods of assay and of clinical tests are brief but adequate for an understanding of the principles employed. The table of the vitamin values of foods is expressed in international units per ounce. Such figures are particularly helpful in a comparison of specific foods for their vitamin content and permit an estimation of the adequacy of vitamins in ordinary servings.

The book contains not only many typographic errors, omission and transposition of letters, but errors as to references, such as that to Wald on page 34. However, much information is given that is not available elsewhere under one cover.

Concepts and Problems of Psychotherapy. By Leland E. Hinsie, M.D., Professor of Clinical Psychiatry, College of Physicians and Surgeons, Columbia University; Assistant Director, New York State Psychiatric Institute and Hospital. Preface by Nolan D. C. Lewis, Neurological Institute of New York. Price, $2.75. Pp. 199, with 1 chart and 5 tables. New York: Columbia University Press, 1937.

Considering the numerous semipopular treatises written today, chiefly representing unhappy attempts to clarify the theories of Freud, it is a pleasant surprise to find a clear, concise though greatly abridged study of four modern methods of psychiatric therapy. In the first 154 pages of his book Hinsie attempts to present and evaluate these four concepts of psychotherapy, namely (1) the psychoanalysis of Freud, (2) the psychobiology of Meyer, (3) the individual psychology of Adler and (4) the analytic psychology of Jung. The major portion of the book is devoted to Freud's theories, many of which are simplified and explained for the benefit of the reader. The author gives favorable and unfavorable criticisms of each method of psychotherapy that he presents, based on his own clinical experience and on data from numerous other sources.

There is a chapter on the statistical evaluation of psychotherapeutic methods by Dr. Carney Landis, who admits that at present statistical methods applied to therapeutic results in mental disease are hindered because the essential nature and

cause of the disease are unknown in the majority of cases, there is often disagreement of opinion among those qualified to know regarding the diagnosis and there is no uniformity of opinion with respect to usage of such terms as cured, recovered and improved, as applied in psychopathologic cases. Hinsie pleads for a greater application of statistical methods to psychotherapeutic procedures in order to make better evaluation possible. He presents data showing how statistics have resulted in aiding and developing methods of therapy in other special medical fields.

Undoubtedly students and specialists in the various branches of psychotherapy will criticize Hinsie's book for its brevity in their particular fields. However, there is no question that the book will serve as an excellent textbook for beginners in psychiatry and for those physicians in other special medical fields or in general practice who would like to gain some insight into modern psychotherapy.

Biological and Clinical Chemistry. By Matthew Steel, Ph.D. Price, $8. Pp. 770, with 21 illustrations. Philadelphia: Lea & Febiger, 1937.

This is a new textbook of physiologic chemistry, written expressly for medical students. It is intended to be used both as a classroom textbook and as a laboratory manual. In fulfilment of the latter aim, 268 experiments are described, which provide a comprehensive laboratory course. These are clearly outlined and are in the modern manner, in that the student is expected to use himself and his fellows for testing as often as he uses animals and chemicals.

The didactic portions, however, are subdivided in an unusual manner as regards emphasis on different phases of biochemistry. For example, 103 pages are devoted to physical chemistry and the biophysics of cells and tissues; 109 pages, to biochemical catalysts (enzymes), vitamins and hormones; 75 pages, to the chemistry of the blood, of which 28 are devoted to methods and experiments, and 48 pages, to the urine and the excretory process, of which about one third contain experiments. Nutrition, energy metabolism and carbohydrate metabolism are discussed in considerably less than 50 pages each. The physicochemical material and the organic chemistry (carbohydrates, lipids and proteins) are well described, even though one questions the necessity of some of the biophysics in a medical curriculum. On the other hand, the intermediate metabolism, in general, is presented superficially. The presentation of the acid-base balance is inadequate, and many recent contributions to human biochemistry are neglected.

The general tone of the clinical correlations may be detected from this excerpt from page 675:

"Since a man should consume 300 to 400 grams of glucose, or its equivalent in carbohydrate, a very severe diabetic will require *150* to *200* [italics not in text] units of insulin daily distributed in doses of 30 to 40 units five times a day."

There are many errors throughout, not all of which are typographic. Some proper names are rendered in a variety of ways, but the most startling is the designation of the late great nutritionist as Graham Lust (page 607).

Each chapter is terminated by a short but apparently satisfactory list of special and general references.

Cirurgia das glandulas parathyroides; anatomia cirurgica; technica indicações; modo de acção. By Sardinha Xavier da Silveira. Pp. 105, with 34 illustrations. Rio de Janeiro, 1936.

This monograph on the parathyroid glands consists chiefly of a review of the literature. In addition to a historical account of surgery of the parathyroid glands, the author and her co-workers have reviewed the reports of 1,052 cases in the literature, consisting of studies of cadavers, as to the variations in number, location and blood supply of the parathyroid glands. Seventy per cent of the patients were found to have the normal number—four. Less than four were found in 28 per cent. Anomalies of location were observed in 1.5 per cent.

The review of calcium metabolism and surgical technic presents no new findings. The discussion of parathyroidectomy for scleroderma and thrombo-angiitis obliterans presents several interesting aspects. The author reports continued improvement after one year in a patient with scleroderma, a Brazilian woman who underwent parathyroidectomy.

The observations in the single case of scleroderma, according to the author, confirmed the findings of Leriche, Jung and Sureyya, Seyle, Shelling, Ashes and Jackson on the interrelation of scleroderma and parathyroid dysfunction. Leriche found that 70 per cent of the patients with scleroderma had hypercalcemia. Hypercalcemia was also observed in the case reported on by the author.

Three patients with thrombo-angiitis obliterans treated by parathyroidectomy are reported on. Illustrations of the improvement in the lesions of the extremities accompany the discussion. Increased vasodilatation, increased temperature of the extremities, diminished pain and a lowered calcium level of the blood were some of the effects observed. These findings confirm, according to the author, those of Welti, of Paris, who has previously reported the use of parathyroidectomy as a therapeutic procedure in Buerger's disease. The condition is attributed to hypertonia of the sympathetic nervous system due to hypercalcemia.

Lehrbuch der Elektrokardiographie. By David Scherf, M.D. Second edition. Price, 18 marks. Pp. 264, with 186 illustrations. Vienna: Julius Springer, 1937.

This book represents a systematic approach to the understanding of electrocardiography in health and disease. It is simply written, and the electrocardiographic changes are described so that the beginner may gain an understanding of them with only a general background of cardiologic training. The outline is much the same as that in similar textbooks. The physiology of impulse conduction and the development of the electrical potential lead up to a consideration of the principles of the recording unit, a résumé of the anatomy and physiology of the specific myocardium and then a discussion of normal and abnormal electrocardiograms. The newer advances in electrocardiography are given. Both nomenclatures for bundle branch block are outlined. Thoracic leads are discussed. The differentiation of the curves in cases of pericarditis and coronary thrombosis is clearly given, and the confusion with pulmonary embolus is pointed out. A discussion of the bundle of Kent is included.

The second edition of this textbook has followed the first after only eight months. The reviewer has not seen the first edition, but, according to the author's statement, in the second edition the contents have been enlarged, and the newer literature has been taken into consideration.

A bibliography is appended to each section.

Les gastropathies des syphilitiques. By Carlos Bonorino Udaondo. Preface by Émile Sergent. Paper. Price, 32 francs. Pp. 216, with 19 illustrations Paris: Masson & Cie, 1936.

This is a well written monograph dealing with syphilitic lesions of the stomach. Little original work is presented, but the subject is extensively reviewed. The bibliography contains 537 references. The author clearly states that his purpose in preparing the review was to clarify some of the more important diagnostic points of gastric syphilis and not to emphasize the occurrence of such lesions. Collecting data reported by twenty-three writers since the publication of Chiari's report in 1885, he compares the relative incidence of proved syphilitic lesions of the stomach according to: (1) the incidence with regard to other gastric conditions, (2) the incidence in known syphilitic patients, and (3) the postmortem incidence of syphilis of the stomach. The author reviewed the various available classifications of gastric lesions of syphilitic origin and presents a simple but complete original classification, which should prove of merit. The major portion

of the monograph deals with the anatomic, roentgenographic laboratory and clinical findings of diagnostic value for each of the entities according to his classification. The material and method of presentation should prove of interest to those who are desirous of a fairly concise readable review of the subject.

Atlas of Hematology. By Edwin E. Osgood, M.D., Assistant Professor of Medicine and Head of Experimental Medicine, University of Oregon Medical School, Portland, Ore., and Clarice M. Ashworth, Medical Illustrator, University of Oregon Medical School, Portland, Ore. Cloth. Price, $10. Pp. 255, with 326 illustrations in color. San Francisco: J. W. Stacy, Inc., 1937.

An atlas is defined as "a volume of plates illustrating any subject." Judged by this definition, this atlas of hematology generously fulfils the requirements.

The book is divided into two general sections. The first part illustrates the various cells that may be found in the circulating blood and in the marrow and includes a description of the parasites which infest the blood. The second part deals with the diseases that are accompanied with characteristic changes in the blood picture. The diseases are dealt with in a somewhat abbreviated fashion as the book does not purport to be a treatise on diseases of the blood. It is offered to those who wish to gain proficiency in recognizing the cells that appear in the blood and marrow in normal and all pathologic conditions. To this end the book leaves little to be desired.

The cells are exceedingly well reproduced, and the color photography is excellent.

The authors describe a simple method by means of which any one with the most elementary knowledge of the subject should be able to identify almost any cell to be found on a well stained slide, even if he has never before seen such a cell. The book is characterized by its simplicity, and simplicity is always a sign of complete familiarity with the subject in hand.

There is a short chapter on laboratory methods, including the authors' technic for sternal puncture, and there is an excellent bibliography.

To the hematologist the book may appear elementary, but good hematologists are not numerous. For clinicians, students and technicians, to whom the book is primarily offered, it will most adequately perform its allotted task.

It is rather unfortunate that the authors have thought it advisable to propose a new nomenclature. The old established nomenclature has served a good purpose for a long time, and while the new terms offered in this work may be pleasing to the philologist, they are likely to be confusing to the clinician and student.

Christian R. Holmes, Man and Physician. By Martin Fischer. Price, $4. Pp. 233. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

This presentation of the life of Dr. Christian R. Holmes includes a short discussion of his childhood, adolescent and college years and a more complete dissertation on his professional years. Fischer includes a detailed survey of Holmes' contributions to the medical development of Cincinnati. His ceaseless work in collecting funds, municipal grants and endowments for the construction, furnishing and adequate staffing of the Cincinnati General Hospital and Cincinnati Medical School is outstanding. His untiring aggressiveness was responsible for his success in achieving the desired ends, in spite of the corrupt political situation that existed in the city at that time. The book includes not only biographic material but a great deal of interesting historical information concerning the medical and political life of Cincinnati.

The book is well planned and lucidly and interestingly written. The large print on dull-finished paper is welcomed. Many proverbial remarks and the few illustrations that supplement the main presentation add to the value of the book.

This biography of Holmes offers enjoyable and instructive reading material concerning a man of whom the members of the medical profession and the laymen not only of Cincinnati but of America should be proud.